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Use of Trace Elements and Halotherapy in the Treatment of Human Diseases

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1. Introduction

Trace elements possess important therapeutic properties. First, binding to specific macromolecules (enzymes, nucleic acids, etc.) they influence important chemical and biological processes; second, they interact amongst themselves synergistically to amplify their individual reactions. Some trace elements are also metals. Not all metals are trace elements. Metals have been used therapeutically for hundreds of years. Use of metals in the treatment of human diseases began with discoveries with gold used initially in patients with tuberculosis followed by rheumatoid arthritis. Gold identified an immunological pathogenesis in the etiology of rheumatoid arthritis, thus metals may be efficacious in other human conditions that are immunological in etiology. The antineoplastic potential of metals was further disseminated by the development of less toxic compounds such as platinum. Third, use of metals in the treatment of human cancers has improved the therapeutic effectiveness response to this diverse group of diseases. Fourth, lithium use in clinical medicine revolutionized treating psychiatric mood disorders. Central to the biological action of lithium is its ability to influence brain and central nervous system chemistry, thereby providing spectacular results in the treatment of affective and other psychiatric mood disorders, in particular, suicide prevention. Discoveries defining alternative non-psychiatric clinical use of lithium continue to intrigue clinical medicine based upon a key discovery demonstrating lithium can effectively influence stem cells. Halotherapy is using salt compounds as initial and maintenance therapy of human respiratory ailments. Used by the Greeks and Romans, halotherapy has existed for thousand of years. It is associated with the therapeutic effectiveness attributed to spas. Today halotherapy has gained resurgence with its use as personalized medicine in the treatment of human diseases.

2. Trace elements as medicines

2.1. Role and function as medicine for the treatment of human diseases

Trace element properties are the core of their therapeutic activity based upon their activity in chemical reactions such as binding to macromolecules like enzymes and nucleic acids, inhibiting specific biological reactions, and their interactions with other elements. These general properties, specifically the binding to large molecules are far from specific, which helps explain why their use has gained interest and popularity over the years in a wide range of diseases in which trace elements have been implicated as medicine. Although trace elements as metals have been associated with human use for centuries, the scientific basis for their use as medicines in humans began with the gold compounds, initially in patients with tuberculosis and later in rheumatoid arthritis. Although other drugs have been developed to treat these infectious and inflammatory diseases, gold has retained an important position in the treatment of these diseases especially in certain cultures. Gold-induced effects on the immune system in rheumatoid arthritis are observed in conditions where autoimmune is involved. Trace element metal complexes have been used as anti-cancer therapy. They have been widely used by the development of less toxic compounds such as platinum and possibly other trace elements. Simultaneously there have been improvements in the administration of these compounds. This increases their therapeutic efficacy in the treatment of specific diseases. There are specific types of cancers that respond to trace elements. The gastrointestinal system represents another area where trace elements have a therapeutic role both in the control of intraluminal acidity and nutrient availability. The central nervous system is another area for trace element therapeutics. This involves the use of lithium. Lithium has provided significant results in the treatment of affective, bi-polar and manic disorders. More recently lithium has shown the ability to influence stem cells derived from a number of different sites in the human body. Thus, lithium may also have clinical use in human alignments or injuries such as spinal chord conditions where here-to-fore these patients were committed to a lifetime of paralysis. An example is spinal chord injuries where lithium use with stem cells can improve clinical outcomes in these patients who previously were non-treatable. With a very wide range of other conditions in which they are employed, trace element use provides a compelling illustration of the importance of trace elements in human disease.

2.2. Boron

In the periodic table boron finds its place in group 13 comprising boron, aluminum, gallium, indium, thallium, and ununtrium. Boron group elements are characterized by having three electrons in their outer energy levels (valence layers) [1]. These elements have also been referred to as icosagens and triels [2].

Boron is classified as a metalloid. Boron occurs sparsely, probably because bombardment by the subatomic particles produced from natural radioactivity disrupts its nuclei. Aluminum occurs widely on earth, and is the third most abundant element in the Earth's crust (8.3%)[3]. Gallium is abundant on earth, while Indium is the 61st most abundant element in the earth's

crust. Thallium is found in moderate amounts. Ununtrium is never found in nature and therefore is termed a synthetic element.

Many of the elements found in this group have fundamental roles in biology. Boron is a trace element in humans and is also essential for some plants. Lack of boron can lead to stunted plant growth, while excess boron thus can cause harm by inhibiting growth. Aluminum has neither a biological role nor significant toxicity associated with it and is considered safe. Both indium and gallium can stimulate metabolism with gallium credited with the ability to bind to iron proteins; however, thallium is highly toxic interfering with numerous vital enzymes. When boron was used as a pesticide it contributed to these effects [4].

Boron is a very light element because of its atomic number of five. In nature it is almost never found free thus it is very low in abundance, comprising only 0.001% (10 ppm)[5] of the Earth's crust. It is known to occur in over a hundred different minerals and ores; however, the main source is borax, but it is also found in complex compounds [6]. Areas in the world that mine boron include Argentina, Bolivia, China, Peru, Turkey and the United States. Turkey is by far the most important accounting for around 70% of all boron extracted in the world. For the United States it is the state of California that engages in significant production [7].

Boron is essential for many plants. Plant cells use it for strengthening cell walls. It is classified as a trace element in humans, but there is debate over its significance in human nutrition. The chemistry of boron allows it to form carbohydrate complexes so its role in nutrition in the human body may be more important than previously thought. Boron has also been shown to replace iron in some of its functions, particularly in wound healing [8]. Aluminum has no known biological role in animals or plants. Gallium is not essential for the human body, but it does interact with iron that allows it to become bound to iron bound and transport proteins [9]. Gallium can also stimulate metabolism. Indium and its heavier complexes have no known biological role, although in small amounts like gallium, indium salts can stimulate metabolism [10].

All elements within the boron group can be toxic. Many are only toxic to plants, some only to animals with some to both. An example of boron toxicity is it harms barley in concentrations exceeding 20 mM[11]. In plants the symptoms of boron toxicity are numerous, such as: reduced cell division, decreased shoot and root growth, decreased production of leaf chlorophyll, inhibition of photosynthesis, lowering of stomata conductance, reduced proton extrusion from roots, and deposition of lignin and sub-origin [12].

In human medicine, boron is found in the form of boric acid, which is used as a topical astringent and as an ophthalmologic irrigant. Sodium borate is bacteriostatic and commonly added to cold creams, washes, and mouth rinses. Boron compounds found in over-the-counter supplements are reported to enhance mental attentiveness from studies that found alterations in the electroencephalogram in the presence of a low-boron diet. These studies reported also that there's a correlation between a low-boron diet and a decrease in mental alertness. There is no evidence however, that diet supplementations of boron compounds, above the levels derived from a normal balanced diet can enhance mental acuity or improve alertness. When

sprinkled in crevices and corners, boric acid powder controls rodents and insects. Boron compounds are used to enhance the cytotoxicity associated with the use of radiation therapy.

2.3. Calcium

Calcium (Ca) with the atomic number of 20 is a soft gray alkaline earth metal that is the 5th most abundant element by mass found in the earth. Calcium is also the fifth-most-abundant dissolved ion both molarity and mass in seawater, following sodium, chloride, magnesium, and sulfate [13]. For living organisms calcium is essential, in particular where movement of the cytoplasmic calcium ion Ca^{2+} into and out of functions as a signal for many cellular processes.

Calcium salts are colorless. As with magnesium salts and other alkaline earth metal salts, calcium salts are often quite soluble in water. Notable exceptions include the hydroxides such as the sulfates, carbonates and phosphates. When in solution, the calcium ion to the human taste varies remarkably, being reported as mildly salty, sour, "mineral like" or even "soothing." It is apparent that many animals can taste, or develop a taste, for calcium, and use this sense to detect the mineral in a variety of locations and sources [14]. In human nutrition, soluble calcium salts may be added to tart juices without much effect to the average palate.

Calcium is the fifth-most-abundant element by mass in the human body, where it is a common cellular ionic messenger with many functions like enzymes. It also serves as a structural element in bone. It has a relatively high atomic number. Calcium in the skeleton causes bone to be radio-opaque. The human body's solid components following drying or burning of organics, as an example observed following cremation, contributes to about a third of the total "mineral" mass remaining in the body. Approximately one kilogram of calcium is composed in the average skeleton with the remaining mineral content being composed of mostly phosphorus and oxygen.

Calcium should be a very important component of the human diet and is a mineral necessary for life. The National Osteoporosis Foundation states that calcium should play an important role in building stronger, denser bones both early in life and in keeping bones strong and healthy later in adulthood. Approximately 99 percent of the body's calcium is stored in the bones and teeth [15]. In the body calcium has other important uses such as in exocytosis, specifically in neurotransmitter release, and muscle contraction. In the electrical system of the heart, calcium replaces sodium as the mineral that depolarizes the cell, proliferating the action potential. In cardiac muscle, sodium influx initiates an action potential, but during the efflux of potassium, the cardiac myocyte experiences calcium influx, prolonging the action potential and creating a plateau phase of dynamic equilibrium. Long-term deficiency of calcium can lead to rickets and poor blood clotting and in menopausal women it can lead to osteoporosis, where the bone deteriorates creating an increased risk of fractures. While lifelong calcium deficits can affect bone and tooth formation, over-retention causes an increase in blood calcium called hypercalcemia, impaired kidney function and decreased absorption of other minerals [16, 17]. Sources suggest there's a correlation between high calcium intake (2000 mg per day, or twice the U.S. recommended daily allowance, equivalent to six or more glasses of milk per day) and prostate cancer [18]. High calcium intakes or absorption were previously thought to

contribute to the development of kidney stones; however, high calcium intake has been associated with a lower risk for kidney stones in more recent research [19-21], because Vitamin D is required to absorb calcium.

Milk and cheese as dairy products are well-known sources of calcium. Some individuals are allergic to dairy products. There are people who are lactose-intolerant leaving them unable to consume non-fermented dairy products in quantities larger than about half a liter per serving. Others, especially vegans avoid dairy products for ethical and health reasons.

Many good vegetable sources of calcium exist as in seaweeds such as kelp, wakame, and hijiki; nuts and seeds like almonds, hazelnuts, sesame, pistachios, molasses, soy beans, figs, quinoa, okra, rutabaga, broccoli, dandelion leaves, and kale. In addition, for some drinks like soymilk or orange juice, it is typical to be fortified with calcium. Numerous vegetables, notably spinach, chard, and rhubarb have high calcium content, but they may also contain varying amounts of oxalic acid that binds calcium and reduces its absorption. The same problem may to a degree affect the absorption of calcium from amaranth, collard and chicory greens. This process may also be related to the generation of calcium oxalate. An overlooked source of calcium is eggshell, which can be ground into a powder and mixed into food or a glass of water [22-24]. The calcium content of most foods can be found in the USDA National Nutrient Database [25].

Calcium supplements are used to prevent and to treat calcium deficiencies. Office of Dietary Supplements (National Institutes of Health) recommends that no more than 600 mg of supplement should be taken at a time because the percent of calcium absorbed decreases as the amount of calcium in the supplement increases [26]. It is therefore recommended to spread doses throughout the day [27]. Recommended daily calcium intake for adult's ranges from 1000 to 1300 mg [27]. Calcium supplements may have side effects such as bloating and constipation in some people. It is suggested that taking the supplements with food may aid in nullifying these side effects [27]. Vitamin D is added to some calcium supplements. Proper vitamin D status is important because vitamin D is converted to a hormone in the body, which then induces the synthesis of intestinal proteins responsible for calcium absorption [28].

A study investigating the effects of personal calcium supplement use on cardiovascular risk was reported in the Women's Health Initiative Calcium/Vitamin D Supplementation Study (WHI CaD Study) found a modestly increased risk of cardiovascular events, particularly myocardial infarction in postmenopausal women. A broad recommendation of calcium/vitamin D supplements is therefore not warranted. In osteoporosis such studies often do not test calcium alone, but rather combinations of calcium and vitamin D. Randomized controlled clinical trials found both positive [29] and negative [30-33] effects. The different results may be explained by doses of calcium and underlying rates of calcium supplementation in the control groups [34]. A meta-analysis [35] by the international Cochrane Collaboration of two randomized controlled trials [36-37] found that calcium "might contribute to a moderate degree to the prevention of adenomatous colonic polyps. More recent studies were conflicting, and one that was positive for effect did control for a possible anti-carcinogenic effect of vitamin D, which was found to be an independent positive influence from calcium-alone on cancer risk [38].

A randomized controlled trial found that 1000 mg of elemental calcium and 400 IU of vitamin D₃ had no effect on colorectal cancer [39]. A randomized controlled trial found that 1400–1500 mg supplemental calcium and 1100 IU vitamin D₃ reduced aggregated cancers with a relative risk of 0.402 [40]. An observational cohort study found that high calcium and vitamin D intake was associated with lower risk of developing premenopausal breast cancer [41].

Compared with other metals, the calcium ion and most calcium compounds have low toxicity. This is not surprising given the very high natural abundance of calcium compounds in the environment and in organisms. Calcium poses few serious environmental problems, with kidney stones the most common side effect in clinical studies. Acute calcium poisoning is rare, and difficult to achieve unless calcium compounds are administered intravenously. For example, the oral median lethal dose (LD₅₀) for rats for calcium carbonate and calcium chloride are 6.45 [42] and 1.4 g/kg [43] respectively.

Calcium metal is hazardous because of its sometimes-violent reactions with water and acids. Calcium metal is found in some drain cleaners where it functions to generate heat and calcium hydroxide that saponifies fats and liquefies proteins, e.g., hair that block drains. When swallowed calcium metal has the same effect on the mouth, esophagus and stomach, and can be fatal [44].

Excessive consumption of calcium carbonate antacids/dietary supplements, over a period of weeks or months can cause milk-alkali syndrome with symptoms ranging from hypercalcemia to potentially fatal renal failure. What constitutes “excessive” consumption is not well known and, it is presumed, varies a great deal from person to person. Persons consuming more than 10 grams/day of CaCO₃ (=4 g Ca) are at risk of developing milk-alkali syndrome [45], but the condition has been reported in at least one person consuming only 2.5 grams/day of CaCO₃ (=1 g Ca), an amount usually considered moderate and safe [46]. Oral calcium supplements diminish the absorption of thyroxine when taken within four to six hours of each other [47]. Thus, people taking both calcium and thyroxine run the risk of inadequate thyroid hormone replacement and thence hypothyroidism if they take them simultaneously or near-simultaneously [48]. Excessive calcium supplementation can be detrimental to cardiovascular health, especially in men [49, 50].

2.4. Chromium

Trivalent chromium (Cr (III) or Cr³⁺) occurs in trace amounts in foods and waters, and appears to be benign [51]. In contrast, hexavalent chromium (Cr (VI) or Cr⁶⁺) is very toxic and mutagenic when inhaled. Cr (VI) has not been established as a carcinogen when in solution, although it may cause allergic contact dermatitis (ACD) [52].

Chromium deficiency, involving a lack of Cr (III) in the body, or perhaps some complex of it, such as glucose tolerance factor is controversial, or is at least extremely rare. Chromium has no verified biological role and has been classified by some as *not* essential for mammals [53]. However, other reviews have regarded it as an essential trace element in humans [54]. It is a reddish crystalline powder, 12.5% Cr (III) by weight, very sparingly soluble in water. Chromium deficiency has been attributed to only three people on long-

term parenteral nutrition, which is when a patient is fed a liquid diet through intravenous drips for long periods of time [55].

Although no biological role for chromium has ever been demonstrated, dietary supplements for chromium include chromium (III), chromium (III) picolinate, chromium (III) polynicotinate, and related materials. The benefit of those supplements is questioned by some studies [56]. The use of chromium-containing dietary supplements is controversial, owing to the absence of any verified biological role, the expense of these supplements, and the complex effects of their use [57]. The popular dietary supplement chromium picolinate, complex generates chromosome damage in hamster cells (due to the picolinate ligand) [58]. In the United States the dietary guidelines for daily chromium uptake were lowered in 2001 from 50–200 µg for an adult to 35 µg (adult male) and to 25 µg (adult female)[59].

No comprehensive, reliable database of chromium content of food currently exists [60]. Data reported prior to 1980 is unreliable due to analytical error [56]. Chromium content of food varies widely due to differences in soil mineral content, growing season, plant cultivar, and contamination during processing. [60]. In addition, large amounts of chromium (and nickel) leech into food cooked in stainless steel [61,62].

The acute oral toxicity for chromium (VI) ranges between 50 and 150 µg/kg [61]. In the body, chromium (VI) is reduced by several mechanisms to chromium (III) already in the blood before it enters the cells. The chromium (III) is excreted from the body, whereas the chromate ion is transferred into the cell by a transport mechanism, by which also sulfate and phosphate ions enter the cell. The acute toxicity of chromium (VI) is due to its strong oxidational properties. After it reaches the blood stream, it damages the kidneys, the liver and blood cells through oxidation reactions. Hemolysis, renal and liver failure are the results of these damages. Aggressive dialysis can improve the situation [63].

The carcinogenicity of chromate dust has been known for a long time. In 1890 the first publication described the elevated cancer risk of workers in a chromate dye company [64,65]. Three mechanisms have been proposed to describe the genotoxicity of chromium (VI). The first mechanism includes highly reactive hydroxyl radicals and other reactive radicals that are by products of the reduction of chromium (VI) to chromium (III). The second process includes the direct binding of chromium (V), produced by reduction in the cell, and chromium (IV) compounds to DNA. The last mechanism attributed the genotoxicity to the binding to the DNA of the end product of the chromium (III) reduction [66].

In some people chromium salts (chromates) are also the cause of allergic reactions. Chromates are often used to manufacture, amongst other things, leather products, paints, cement, mortar and anti-corrosives. Contact with products containing chromates can lead to allergic contact dermatitis and irritant dermatitis, resulting in ulceration of the skin, sometimes referred to as "chrome ulcers". This condition is often found in workers that have been exposed to strong chromate solutions in electroplating, tanning and chrome-producing manufacturers [67,68]. As chromium compounds were used in dyes and paints and leather tanning, these compounds are often found in soil and groundwater at abandoned industrial sites that now need envi-

ronmental cleanup and remediation of contaminated land. Primer paint containing hexavalent chromium is still widely used for aerospace and automobile refinishing applications [69].

2.5. Copper

Copper is essential to all living organisms as a trace dietary mineral because it is a key constituent of the respiratory enzyme complex cytochrome c oxidase. In mollusks and crustacean copper is a constituent of the blood pigment hemocyanin, which is replaced by the iron-complexed hemoglobin in fish and other vertebrates. The main areas where copper is found in humans are liver, muscle and bone [70]. Copper compounds are used as bacteriostatic substances, fungicides and wood preservatives. Numerous antimicrobial efficacy studies have been conducted in the past 10 years regarding copper's efficacy to destroy a wide range of bacteria, as well as influenza A virus, adenovirus, and fungi [93].

Copper-alloy touch surfaces have natural intrinsic properties to destroy a wide range of microorganisms, *E.coli*, methicillin-resistant *Staphylococcus aureus*, influenza A virus, adenovirus, and fungi [71]. Some 355 copper alloys were proven to kill more than 99.9% of disease-causing bacteria within just two hours when cleaned regularly [72]. The U.S. Environmental Protection Agency (EPA) has approved the registrations of these copper alloys as antimicrobial materials with public health benefits [72], which allows manufacturers to legally make claims as to the positive public health benefits of products made with registered antimicrobial copper alloys. In addition, the EPA has approved a long list of antimicrobial copper products made from these alloys, such as bedrails, handrails, over-bed tables, sinks, faucets, door knobs, toilet hardware, computer keyboards, health club equipment, shopping cart handles, etc. (for a comprehensive list of products. Copper doorknobs are used by hospitals to reduce the transfer of disease and Legionnaires' disease is suppressed by copper tubing in plumbing systems [73]. Antimicrobial copper alloy products are now being installed in healthcare facilities in the U.K., Ireland, Japan, Korea, France, Denmark, and Brazil and in the subway transit system in Santiago, Chile, where copper-zinc alloy handrails will be installed in some 30 stations by 2014 [74-76].

Copper proteins have diverse roles in biological electron transport and oxygen transportation, processes that exploit the easy interconversion of Cu (I) and Cu (II) [77-79]. The biological role for copper commenced with the appearance of oxygen in earth's atmosphere [80]. The protein hemocyanin is the oxygen carrier in most mollusks and some arthropods such as the horseshoe crab (*Limulus polyphemus*) [81]. Because hemocyanin is blue, these organisms have blue blood, not the red blood found in organisms that rely on hemoglobin for this purpose. Structurally related to hemocyanin are the lactases and tyrosinases. Instead of reversibly binding oxygen, these proteins hydroxylate substrates, illustrated by their role in the formation of lacquers [79].

Copper is also a component of other proteins associated with the processing of oxygen. In cytochrome c oxidase, which is required for aerobic respiration, copper and iron cooperate in the reduction of oxygen. Copper is also found in many superoxide dismutases, proteins that catalyze the decomposition of superoxides, by converting it to oxygen and hydrogen peroxide:



Several copper proteins, such as the "blue copper proteins" do not interact directly with substrates hence they are not enzymes. These proteins relay electrons by the process called electron transfer [79].

Copper is an essential trace element in plants and animals, but not in some microorganisms. The human body contains copper at a level of about 1.4 to 2.1 mg per kg of body mass [82]. Stated differently, the recommended daily allowance (RDA) for copper in normal healthy adults is quoted in the range of 0.97 mg/day to 3.0 mg/day [83]. Copper is absorbed in the gut, and then transported to the liver then bound to albumin [84]. After processing in the liver, copper is distributed to other tissues in a second phase. Copper transport here involves the protein ceruloplasmin, which carries the majority of copper in blood. Ceruloplasmin also carries copper that is excreted in milk, and is particularly well absorbed as a copper source [85]. Copper in the body normally undergoes enterohepatic circulation (about 5 mg a day, vs. about 1 mg per day absorbed in the diet and excreted from the body), and the body is able to excrete some excess copper, if needed, via bile, which carries some copper out of the liver that is not then reabsorbed by the intestine [84,85].

Because of its role in facilitating iron uptake, copper deficiency can produce anemia-like symptoms, neutropenia, bone abnormalities, hypopigmentation, impaired growth, increased incidence of infections, osteoporosis, hyperthyroidism, and abnormalities in glucose and cholesterol metabolism. Conversely, Wilson's disease causes an accumulation of copper in body tissues. Severe deficiency can be found by testing for low plasma or serum copper levels, low ceruloplasmin, and low red blood cell superoxide dismutase levels; these are not sensitive to marginal copper status. The cytochrome c oxidase activity of leucocytes and platelets has been stated as another factor in deficiency, but the results have not been confirmed by replication [86].

Gram quantities of various copper salts have been taken in suicide attempts and produced acute copper toxicity in humans, possibly due to redox cycling and the generation of reactive oxygen species that damage DNA [87,88]. Corresponding amounts of copper salts (30 mg/kg) are toxic in animals [89]. A minimum dietary value for healthy growth in rabbits has been reported to be at least 3 ppm in the diet [90]. However, higher concentrations of copper (100 ppm, 200 ppm, or 500 ppm) in the diet of rabbits may favorably influence feed conversion ratio, growth rates, and carcass dressing percentages [91].

Chronic copper toxicity does not normally occur in humans because of transport systems that regulate absorption and excretion. Autosomal recessive mutations in copper transport proteins can disable these systems, leading to Wilson's disease with copper accumulation and cirrhosis of the liver in persons who have inherited two defective genes [82].

2.6. Gold

Gold is a chemical element with the symbol Au and atomic number 79. It is a dense, soft, malleable, and ductile metal with an attractive, bright yellow color and luster that is maintained without tarnishing in air or water. Chemically, gold is a transition metal and a group 11 element. It is one of the least reactive chemical elements, solid under standard conditions. The metal therefore occurs often in free elemental form, as nuggets or grains in rocks, in veins and in alluvial deposits. Less commonly, it occurs in minerals as gold compounds, such as with tellurium as calaverite, sylvanite and krennerite. Gold is perhaps the most anciently administered medicine [92] and known to the ancients [93-94] with apparent paradoxes with respect to its toxicology. This information suggests there are still serious gaps in understanding of action of gold on physiology [95].

In medieval times, gold was often seen as beneficial for the health, in the belief that something so rare and beautiful could not be anything but healthy. Even some modern esotericists and forms of alternative medicine assign metallic gold a healing power [96]. Some gold salts do have anti-inflammatory properties and are used as pharmaceuticals in the treatment of arthritis and other similar conditions. Gold-based injections have been explored as a means to help to reduce the pain and swelling of rheumatoid arthritis and tuberculosis [97]. However, only salts and radioisotopes of gold are of pharmacological value, as elemental (metallic) gold is inert to all chemicals it encounters inside the body.

Gold alloys are used in restorative dentistry, especially in tooth restorations, such as crowns and permanent bridges. The gold alloys' slight malleability facilitates the creation of a superior molar mating surface with other teeth and produces results that are generally more satisfactory than those produced by the creation of porcelain crowns. The use of gold crowns in more prominent teeth such as incisors is favored in some cultures and discouraged in others.

Colloidal gold preparations, such as the use of gold in nanoparticle suspensions in water are intensely red-colored, and can be made with tightly controlled particle sizes up to a few tens of nanometers across by reduction of gold chloride with citrate or ascorbate ions. Colloidal gold is used in research applications in medicine, biology and materials science. The technique of immunogold labeling exploits the ability of the gold particles to adsorb protein molecules onto their surfaces. Colloidal gold particles coated with specific antibodies can be used as probes for the presence and position of antigens on the surfaces of cells [98]. In ultrathin sections of tissues viewed by electron microscopy, the immunogold labels appear as extremely dense round spots at the position of the antigen [99].

Gold, or alloys of gold and palladium are applied as conductive coating to biological specimens and other non-conducting materials such as plastics and glass to be viewed in a scanning electron microscope. The coating, which is usually applied by sputtering with argon plasma, has a triple role in this application. Gold's very high electrical conductivity drains an electrical charge; therefore, its very high density provides stopping power for electrons in the electron beam, helping to limit the depth to which the electron beam penetrates the specimen. This improves definition of the position and topography of the specimen surface and increases the spatial resolution of the image. Gold also produces a high output of secondary electrons when

irradiated by an electron beam, and these low-energy electrons are the most commonly used signal source in the scanning electron microscope [100]. The isotope gold-198 (half-life 2.7 days) is used in nuclear medicine, in some cancer treatments and for treating other diseases [101,102].

2.7. Iodine

Iodine and its compounds are primarily used in nutrition, and industrially in the production of acetic acid and certain polymers. Iodine's relatively high atomic number, low toxicity, and ease of attachment to organic compounds have made it a part of many X-ray contrast materials in modern medicine. Iodine has only one stable isotope. A number of iodine radioisotopes are also used in medical applications.

Iodine is found on Earth mainly as the highly water-soluble iodide ion I^- that concentrates it in oceans and brine pools. Like the other halogens, free iodine occurs mainly as a diatomic molecule I_2 , and then only momentarily after being oxidized from iodide by an oxidant like free oxygen. In the universe and on Earth, iodine's high atomic number makes it a relatively rare element. However, its presence in ocean water has given it a role in biology. It is the heaviest essential element utilized widely by life in biological functions. Iodine's rarity in many soils, due to initial low abundance as a crust-element, and also leaching of soluble iodide by rainwater, has led to many deficiency problems in land animals and inland human populations. Iodine deficiency affects about two billion people and is the leading preventable cause of intellectual disabilities [103].

Iodine is required by higher animals, which use it to synthesize thyroid hormones, which contain the element. Because of this function, radioisotopes of iodine are concentrated in the thyroid gland along with nonradioactive iodine. If inhaled, the radioisotope iodine-131, which has a high fission yield, concentrates in the thyroid, but is easily remedied with non-radioactive potassium iodide treatment.

Potassium iodide has been used as an expectorant, although this use is increasingly uncommon. In medicine, potassium iodide is usually used to treat acute thyrotoxicosis, usually as a saturated solution of potassium iodide. It is also used to block uptake of iodine-131 in the thyroid gland when this isotope is used as part of radiopharmaceuticals (such as iobenguane) that are not targeted to the thyroid or thyroid-type tissues.

Iodine-131, in the chemical form of iodide is a component of nuclear fallout and a particularly dangerous one owing to the thyroid gland's propensity to concentrate ingested iodine, where it is kept for periods longer than this isotope's radiological half-life of eight days. For this reason, if people are exposed to a significant amount of environmental radioactive iodine (iodine-131 in fallout), they may be instructed to take non-radioactive potassium iodide tablets. The typical adult dose is one 130 mg tablet per 24 hours, supplying 100 mg (100,000 micrograms) iodine, as iodide ion. Typical daily dose of iodine to maintain normal health is of order 100 micrograms. By ingesting this large amount of non-radioactive iodine, radioactive iodine uptake by the thyroid gland is minimized [104].

Diatrizoic acid, an iodine-containing radio contrast agent Iodine, as an element with high electron density and atomic number absorbs X-rays well. Therefore, it may be used as a radio

contrast agent by filtering out imaging X-rays weaker than 33.3 keV, where iodine's innermost electrons begin absorbing X-rays strongly due to the photoelectric effect [105.] Organic compounds of a certain type (typically iodine-substituted benzene derivatives) are thus used in medicine as X-ray radio contrast agents for intravenous injection. This is often in conjunction with advanced X-ray techniques such as angiography and CT scanning. At present, all water-soluble radio contrast agents rely on iodine.

2.8. Iron

Iron is a chemical element with the symbol Fe (from Latin: *ferrum*) and atomic number 26. It is a metal in the first transition series. It is the most common element (by mass) forming the planet Earth as a whole, forming much of Earth's outer and inner core. It is the fourth most common element in the Earth's crust. Iron's very common presence is due to its abundant production as a result of fusion in high-mass stars, where the production of nickel-56 (which decays to the most common isotope of iron) is the last nuclear fusion reaction that is exothermic. This causes radioactive nickel to become the last element to be produced before collapse of a supernova leads to the explosive events that scatter this precursor radio nucleotide of iron abundantly into space.

Iron is abundant in biology [106]. Iron-proteins are found in all living organisms, ranging from the evolutionarily primitive archaea to humans. The color of blood is due to the hemoglobin, an iron-containing protein. As illustrated by hemoglobin, iron is often bound to cofactors, e.g. in hemes. The iron-sulfur clusters are pervasive and include nitrogenase, the enzymes responsible for biological nitrogen fixation. Influential theories of evolution have invoked a role for iron sulfides in the iron-sulfur world theory.

Structure of heme, in the protein additional ligand would be attached to Fe. Iron is a necessary trace element found in nearly all-living organisms. Iron-containing enzymes and proteins, often containing heme prosthetic groups participate in many biological oxidations and in transport. Examples of proteins found in higher organisms include hemoglobin, cytochrome and catalase [107]. Iron is pervasive, but particularly rich sources of dietary iron include red meat, lentils, beans, poultry, fish, leaf vegetables, watercress, tofu, chickpeas, black-eyed peas, blackstrap molasses, fortified bread, and fortified breakfast cereals. Iron in low amounts is found in molasses, teff and farina. Iron in meat (heme iron) is more easily absorbed than iron in vegetables [108]. Although some studies suggest that heme/hemoglobin from red meat has effects that may increase the likelihood of colorectal cancer [109,110]. There is still some controversy [111] and even a few studies suggesting that there is not enough evidence to support such claims [112].

Iron provided by dietary supplements is often found as iron (II) fumarate, although iron sulfate is cheaper and is absorbed equally well. Elemental iron, or reduced iron, despite being absorbed at only one third to two thirds the efficiency (relative to iron sulfate) [113] is often added to foods such as breakfast cereals or enriched wheat flour. Iron is most available to the body when chelated to amino acids [114] and is also available for use as a common iron supplement. Often the amino acid chosen for this purpose is the cheapest and most common amino acid, glycine, leading to "iron glycinate" supplements [115]. The Recommended Dietary

Allowance (RDA) for iron varies considerably based on age, gender, and source of dietary iron (heme-based iron has higher bioavailability) [116]. Infants may require iron supplements if they are bottle-fed cow's milk [117]. Blood donors and pregnant women are at special risk of low iron levels and are often advised to supplement their iron intake [118]. Iron acquisition poses a problem for aerobic organisms, because ferric iron is poorly soluble near neutral pH. Thus, bacteria have evolved high-affinity sequestering agents called siderophores [119-121].

After uptake, in cells, iron storage is carefully regulated as "free" as iron ions do not exist as free. A major component of this regulation is the protein transferrin, which binds iron ions absorbed from the duodenum and carries it in the blood to cells [122]. In animals, plants, and fungi, iron is often the metal ion incorporated into the heme complex. Heme is an essential component of cytochrome proteins, which mediate redox reactions, and of oxygen carrier proteins such as hemoglobin, myoglobin, and leg hemoglobin.

Inorganic iron contributes to redox reactions in the iron-sulfur clusters of many enzymes, such as nitrogenase involved in the synthesis of ammonia from nitrogen and hydrogen and hydrogenate. Non-heme iron proteins include the enzymes methane monooxygenase oxidizes methane to methanol, ribonucleotide reductase, reduces ribose to deoxyribose in DNA synthesis, hemerythrins involved in oxygen transport and fixation in marine invertebrates, and purple acid phosphatase hydrolysis of phosphate esters. Iron distribution is heavily regulated in mammals, partly because iron ions have a high potential for biological toxicity [123].

Iron uptake is tightly regulated by the human body, which has no regulated physiological means of excreting iron. Only small amounts of iron are lost daily due to mucosal and skin epithelial cell sloughing, so control of iron levels is mostly by regulating uptake [124]. Regulation of iron uptake is impaired in some people as a result of a genetic defect that maps to the HLA-H gene region on chromosome 6. In these people, excessive iron intake can result in iron overload disorders, such as hemochromatosis. Many people have a genetic susceptibility to iron overload without realizing it or being aware of a family history of the problem. For this reason, it is advised that people do not take iron supplements unless they suffer from iron deficiency and have consulted a doctor. Hemochromatosis is estimated to cause disease in between 0.3 and 0.8% of Caucasians [125]. MRI finds that iron accumulates in the hippocampus of the brains of those with Alzheimer's disease and in the substantia nigra of those with Parkinson disease [126].

Large amounts of ingested iron can cause excessive levels of iron in the blood. High blood levels of free ferrous iron react with peroxides to produce free radicals, which are highly reactive and can damage DNA, proteins, lipids, and other cellular components. Thus, iron toxicity occurs when there is free iron in the cell, which generally occurs when iron levels exceed the capacity of transferrin to bind the iron. Damage to the cells of the gastrointestinal tract can also prevent them from regulating iron absorption leading to further increases in blood levels. Iron typically damages cells in the heart, liver, and elsewhere, which can cause significant adverse effects, including coma, metabolic coma, metabolic acidosis, shock, liver failure, coagulopathy, adult respiratory distress syndrome, long-term organ damage, and even death [127]. Humans experience iron toxicity above 20 milligrams of iron for every kilogram

of mass, and 60 milligrams per kilogram is considered a lethal dose [128]. Overconsumption of iron, often the result of children eating large quantities of ferrous sulfate tablets intended for adult consumption, is one of the most common toxicological causes of death in children under six [128]. The Dietary Reference Intake (DRI) lists the Tolerable Upper Intake Level (UL) for adults as 45 mg/day. For children under fourteen years old the UL is 40 mg/day. The medical management of iron toxicity is complicated and can include use of a specific chelating agent called deferoxamine to bind and expel excess iron from the body [127,129].

2.9. Lithium

Lithium (from Greek *lithos* 'stone') is a chemical element with symbol Li and atomic number 3. It is a soft, silver-white metal belonging to the alkali metal group of chemical elements. Under standard conditions it is the lightest metal and the least dense solid element. Like all alkali metals, lithium is highly reactive and flammable. For this reason, it is typically stored in mineral oil. When cut open, lithium exhibits a metallic luster, but contact with moist air corrodes the surface quickly to a dull silvery gray, then black tarnish. Because of its high reactivity lithium never occurs freely in nature, and instead, only appears in compounds, which are usually ionic. Lithium occurs in a number of pegmatite minerals, but due to its solubility as an ion is present in ocean water and is commonly obtained from brines and clay. On a commercial scale, lithium is isolated electrolytically from a mixture of lithium chloride and potassium chloride. Lithium and its compounds have several industrial applications, including heat-resistant glass and ceramics, high strength-to-weight alloys used in aircraft, lithium batteries and lithium-ion batteries. These uses consume more than half of lithium production.

Trace amounts of lithium are present in all organisms. The element serves no apparent vital biological function, since animals and plants survive in good health without it; however, its central role in reproduction has been documented [130]. In the absence of lithium when tested in a number of vertebrate species (fowl, cows and goats) showed an increase in spontaneous abortions amongst these species. In humans lithium administered as any of several lithium salts has proved to be useful as a mood-stabilizing drug in the treatment of bipolar disorder due to neurological effects of the ion in the human body [131].

Lithium is found in trace amount in numerous plants, plankton, and invertebrates, at concentrations of 69 to 5,760 parts per billion (ppb). In vertebrates the concentration is slightly lower, and nearly all vertebrate tissue and body fluids have been found to contain lithium ranging from 21 to 763 ppb [132]. Marine organisms tend to bioaccumulate lithium more than terrestrial ones [133]. It is not known whether lithium has a physiological role in any of these organisms [132], but nutritional studies in mammals have indicated its importance to health, leading to a suggestion that it be classed as an essential trace element with an RDA of 1 mg/day [134]. Observational studies in Japan, reported in 2011, suggested that naturally occurring lithium in drinking water might increase human lifespan [135].

Lithium is useful in the treatment of bipolar disorder [136]. Lithium salts may also be helpful for related diagnoses, such as schizoaffective disorder and cyclic major depression. The active part of these salts is the lithium ion Li^+ [137]. They may increase the risk of developing Ebstein's cardiac anomaly in infants born to women who take lithium during the first trimester of

pregnancy [135]. The most exciting results for lithium are its reported non-psychiatric medical effects that are centered on the ion's ability to influence the proliferation of stem cells first identified from hematopoietic tissues [138, 139]. This effect has now been demonstrated to also take place in the regeneration of neurological tissues, thus the use of lithium to treat spinal chord injuries through a mechanism that involves enhancing stem cell regeneration of damaged neurons is very exciting.

2.10. Magnesium

Magnesium is a chemical element with the symbol Mg and atomic number 12. Its common oxidation number is +2. It is an alkaline earth metal and the eighth most abundant element in the Earth's crust and ninth in the known universe as a whole [140]. Magnesium is the fourth most common element in the Earth as a whole (behind iron, oxygen and silicon), making up 13% of the planet's mass and a large fraction of the planet's mantle. The relative abundance of magnesium is related to the fact that it easily builds up in supernova stars from a sequential addition of three helium nuclei to carbon (which in turn is made from three helium nuclei). Due to magnesium ion's high solubility in water, it is the third most abundant element dissolved in seawater [141]. Magnesium is produced in stars larger than 3 solar masses by fusing helium and neon in the alpha process at temperatures above 600 megakelvins.

The free element (metal) is not found naturally on Earth, as it is highly reactive. Once produced, it is coated in a thin layer of oxide, which partly masks this reactivity. The free metal burns with a characteristic brilliant white light, making it a useful ingredient in flares. The metal is now mainly obtained by electrolysis of magnesium salts obtained from brine. Commercially, the chief use for the metal is as an alloying agent to make aluminum-magnesium alloys, sometimes called magnalium or magnelium. Since magnesium is less dense than aluminum these alloys are prized for their relative lightness and strength.

In human physiology, magnesium is the eleventh most abundant element by mass in the human body. Its ions are essential to all living cells, where they play a major role in manipulating important biological polyphosphate compounds like ATP, DNA, and RNA. Hundreds of enzymes thus require magnesium ions to function. Magnesium compounds are used medicinally as common laxatives, and antacids, e.g., milk of magnesia, and in a number of situations where stabilization of abnormal nerve excitation and blood vessel spasm is required (e.g., to treat eclampsia). Magnesium ions are sour to the taste, and in low concentrations they help to impart a natural tartness to fresh mineral waters.

Pharmaceutical preparations of magnesium are used to treat magnesium deficiency and hypomagnesemia, as well as eclampsia [142]. Usually in lower dosages, magnesium is commonly included in dietary mineral preparations, including many multivitamin preparations.

Sorted by type of magnesium salt, biological applications of magnesium include:

- Magnesium sulfate, as the heptahydrate called Epsom salts, is used as bath salts, as a laxative, and as a highly soluble fertilizer [143].

- Magnesium hydroxide, suspended in water, is used in milk of magnesia antacids and laxatives.
- Magnesium chloride, oxide, gluconate, malate, orotate, glycinate and citrate are all used as oral magnesium supplements. Some have claimed that oral magnesium supplements are therapeutic for Restless Leg Syndrome (RLS) in some individuals [144].
- Magnesium borate, magnesium salicylate, and magnesium sulfate are used as antiseptics.
- Magnesium bromide is used as a mild sedative (this action is due to the bromide, not the magnesium).
- Magnesium stearate is a slightly flammable white powder with lubricating properties. In pharmaceutical technology, it is used in the manufacturing of numerous kinds of tablets to prevent the tablets from sticking to the equipment during the tablet compression process (i.e., when the tablet's substance is pressed into tablet form).

Magnesium carbonate powder is used by athletes such as gymnasts, weightlifters and climbers to eliminate moisture and improves the grip on gymnastic apparatus, and lifting and climbing rocks.

Because of the important interaction between phosphate and magnesium ions, magnesium ions are essential to the basic nucleic acid chemistry of life, and thus are essential to all cells of all known living organisms. Over 300 enzymes require the presence of magnesium ions for their catalytic action, including *all* enzymes utilizing or synthesizing ATP, or those that use other nucleotides to synthesize DNA and RNA. ATP exists in cells normally as a chelate of ATP and a magnesium ion.

Plants have an additional use for magnesium in that chlorophylls are magnesium-centered porphyrins. Magnesium deficiency in plants causes late-season yellowing between leaf veins, especially in older leaves, and can be corrected by applying Epsom salts, which is rapidly leached, or else crushed dolomitic limestone to the soil.

Magnesium is a vital component of a healthy human diet. Human magnesium deficiency (including conditions that show few overt symptoms is relatively rare [145], although only 32% of people in the United States meet the RDA-DRI; [146] low levels of magnesium in the body has been associated with the development of a number of human illnesses such as asthma, diabetes, and osteoporosis [147]. Taken in the proper amount magnesium plays a role in preventing both stroke and heart attack. The symptoms of people with fibromyalgia, migraines, and girls going through their premenstrual syndrome are less severe and magnesium can shorten the length of the migraine symptoms [148,149].

Adult human bodies contain about 24 grams of magnesium, with 60% in the skeleton, 39% intracellular (20% in skeletal muscle), and 1% extracellular [150]. Serum levels are typically 0.7–1.0 mmol/L or 1.8–2.4 mEq/L. Serum magnesium levels may appear normal even in cases of underlying intracellular deficiency, although no known mechanism maintains a homeostatic level in the blood other than renal excretion of high blood levels. Intracellular magnesium is correlated with intracellular potassium. Magnesium is absorbed in the gastrointestinal tract,

with more absorbed when status is lower. Magnesium competes with calcium in the human body [151]. In this way it actually keeps calcium in check. However, this can cause a calcium deficiency if calcium levels are already low [152]. Low and high protein intake inhibit magnesium absorption, and other factors such as phosphate, phytate, and fat affect absorption. Absorbed dietary magnesium is largely excreted through the urine, although most magnesium "administered orally" is excreted through the feces [153]. Magnesium status may be assessed roughly through serum and erythrocyte Mg concentrations and urinary and fecal excretion, but intravenous magnesium loading tests are likely the most accurate and practical in most people [154]. In these tests, magnesium is injected intravenously; retention of 20% or more indicates deficiency [155]. Other nutrient deficiencies are identified through biomarkers, but none are established for magnesium [156].

The UK recommended daily values for magnesium is 300 mg for men and 270 mg for women [157.] Spices, nuts, cereals, coffee, cocoa, tea, and vegetables are rich sources of magnesium [158]. Green leafy vegetables such as spinach are also rich in magnesium as they contain chlorophyll. Observations of reduced dietary magnesium intake in modern Western countries compared to earlier generations may be related to food refining and modern fertilizers that contain no magnesium [153].

Numerous pharmaceutical preparations of magnesium, as well as magnesium dietary supplements are available. Magnesium oxide, one of the most common forms in magnesium dietary supplements because it has high magnesium content per weight, has been reported the least bioavailable [159,160]. Magnesium citrate has been reported as more bioavailable than oxide or amino acid chelate forms [161].

Excess magnesium in the blood is freely filtered at the kidneys, and for this reason it is difficult to overdose on magnesium from dietary sources alone [148]. With supplements, overdose is possible, particularly in people with poor renal function; occasionally, with use of high cathartic doses of magnesium salts, severe hypermagnesemia has been reported to occur even without renal dysfunction [162]. Alcoholism can produce a magnesium deficiency, which is easily reversed by oral or parenteral administration, depending on the degree of deficiency [163]. Magnesium concentrations in plasma or serum may be measured to monitor for efficacy and safety in those receiving the drug therapeutically, to confirm the diagnosis in potential poisoning victims or to assist in the forensic investigation in a case of fatal over dosage. The newborn children of mothers who received parenteral magnesium sulfate during labor may exhibit toxicity at serum magnesium levels that were considered appropriate for the mothers [164].

There has been some speculation that magnesium deficiency can lead to depression. Cerebral spinal fluid (CSF) magnesium has been found low in treatment-resistant suicidal depression and in patients that have attempted suicide. Brain magnesium has been found low amounts using phosphorus nuclear magnetic resonance spectroscopy, an accurate means for measuring brain magnesium. Blood and cerebral spinal fluid (CSF) magnesium does not appear well correlated with major depression [165]. Magnesium chloride in relatively small doses was found as effective in the treatment of depressed elderly type 2 diabetics with hypomagnesemia as imipramine 50 mg daily [166].

Results from a meta-analysis of randomized clinical trials demonstrated that magnesium supplementation lowers high blood pressure in a dose dependent manner [167]. Low serum magnesium levels are associated with metabolic syndrome, diabetes mellitus type 2 and hypertension [168]. Low serum magnesium levels have been associated with a higher risk of developing metabolic syndrome [169]. Magnesium therapy is recommended by the 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death for patients with ventricular arrhythmia associated with torsade de pointes that present with long QT syndrome as well as for the treatment of patients with digoxin intoxication-induced arrhythmias [170]. Magnesium is also the drug of choice in the management of pre-eclampsia and eclampsia [171].

Besides its therapeutic role, magnesium has an additional beneficial effect on calcification. Patients with chronic kidney disease have a high prevalence of vascular calcification, and cardiovascular disease is the leading cause of death in this population. Several *in vitro* and animal studies point towards a protective role of magnesium through multiple molecular mechanisms. Magnesium is a natural calcium antagonist and both human and animal studies have shown that low circulating magnesium levels are associated with vascular calcification [172]. Results from an observational study conducted in the general Japanese population demonstrated that lower serum magnesium levels were significantly and independently associated with a greater average intima-media thickness and the risk of at least two carotid plaques [173]. Magnesium supplementation might be useful in reducing the progression of atherosclerosis in chronic dialysis patients [174]. Low serum magnesium may be an independent risk factor for death in patients with chronic kidney disease [175] and patients with mildly elevated serum magnesium levels could have a survival advantage over those with lower magnesium levels [176].

Since the kidneys are responsible for the excretion of magnesium, anyone with a heart or kidney disorder should not take any extra magnesium except under their doctor's supervision. It is very rare to overdose on magnesium from food [152]; however people who ingest large amounts of milk of magnesia (as a laxative or antacid), Epsom Salts (as a laxative or tonic), or magnesium supplements may overdose, especially if they suffer from kidney problems. Too much magnesium can cause several serious health problems, including nausea, vomiting, severely lowered blood pressure, confusion, slowed heart rate, respiratory paralysis, deficiencies of other minerals, coma, cardiac arrhythmia, cardiac arrest, and death. At very high doses, it can even be fatal [152]. However the most common side effects of magnesium toxicity are stomach upset and diarrhea [36].

2.11. Manganese

Manganese is a chemical element designated by the symbol Mn. It has the atomic number 25. It is found as a free element in nature often in combination with iron and in many minerals. Manganese is a metal with important industrial metal alloy uses, particularly in stainless steels. In biology, manganese (II) ions function as cofactors for a large variety of enzymes with many functions [177]. Manganese enzymes are particularly essential in detoxification of superoxide free radicals in organisms that must deal with elemental oxygen. Manganese also functions in

the oxygen-evolving complex of photosynthetic plants. The element is a required trace mineral for all known living organisms. In larger amounts, and apparently with far greater activity by inhalation, it can cause a poisoning syndrome in mammals, with neurological damage, which is sometimes irreversible.

Manganese is an essential trace nutrient in all known forms of life [178]. The classes of enzymes that have manganese cofactors are very broad, and include oxidoreductases, transferases, hydrolases, lyases, isomerases, ligases, lectins, and integrins. Reverse transcriptase found in many retroviruses contains manganese. The best-known manganese-containing polypeptides may be arginase, the diphtheria toxin and Mn-containing superoxide dismutase [179].

Mn-(super oxide dismutase (SOD) is the type of SOD present in eukaryotic mitochondria, and also in most bacteria (this fact is in keeping with the bacterial-origin theory of mitochondria). The Mn-SOD enzyme is probably one of the most ancient, for nearly all organisms living in the presence of oxygen use it to deal with the toxic effects of superoxide, formed from the 1-electron reduction of oxygen. Exceptions include a few kinds of bacteria, and related lactobacilli, which use a different nonenzymatic mechanism, involving manganese (Mn^{2+}) ions complexed with polyphosphate directly for this task, indicating how this function possibly evolved in aerobic life.

The human body contains about 12 mg of manganese, which is stored mainly in the bones; in the tissue, it is mostly concentrated in the liver and kidneys [20]. In the human brain, the manganese is bound to manganese metalloproteins, most notably glutamine synthetase in astrocytes [180]. Manganese is also important in photosynthetic oxygen evolution in chloroplasts in plants. The oxygen-evolving complex (OEC) is a part of photosystem II contained in the thylakoid membranes of chloroplasts; it is responsible for the terminal photo oxidation of water during the light reactions of photosynthesis, and has a metalloenzyme core containing four atoms of manganese [181]. For this reason, most broad-spectrum plant fertilizers contain manganese.

Manganese compounds are less toxic than those of other widespread metals, such as nickel and copper [182]. However, exposure to manganese dusts and fumes should not exceed the ceiling value of 5 mg/m³ even for short periods because of its toxicity level [183]. Manganese poisoning has been linked to impaired motor skills and cognitive disorders [184-186]. In 2005, a study suggested a possible link between manganese inhalation and central nervous system toxicity in rats [187]. The Occupational Safety and Health Administration in the United States regulates exposure to manganese [188]. Generally, exposure to ambient Mn air concentrations in excess of 5 µg Mn/m³ can lead to Mn-induced symptoms. Increased ferroportin protein expression in human embryonic kidney (HEK293) cells is associated with decreased intracellular Mn concentration and attenuated cytotoxicity, characterized by the reversal of Mn-reduced glutamate uptake and diminished lactate leakage [189].

Waterborne manganese has a greater bioavailability than dietary manganese. According to results from a 2010 study [190] higher levels of exposure to manganese in drinking water levels are associated with increased intellectual impairment and reduced intelligence quotients in school-age children. It is hypothesized that long-term exposure to the naturally occurring

manganese in shower water puts up to 8.7 million Americans at risk [191-193]. Manganese overexposure is most frequently associated with manganism, a rare neurological disorder associated with excessive manganese ingestion or inhalation. Historically, persons employed in the production or processing of manganese alloys [194,195] have been at risk for developing manganism; however, current health and safety regulations protect workers in developed nations [158]. The disorder was first described in 1837 by British academic John Couper in two patients who were manganese grinders [196].

Manganism is a biphasic disorder. In its early stages, an intoxicated person may experience depression, mood swings, compulsive behaviors, and psychosis. Early neurological symptoms give way to late-stage manganism, which resembles Parkinson's disease. Symptoms include weakness, monotone and slowed speech, an expressionless face, tremor, forward-leaning gait, inability to walk backwards without falling, rigidity, and general problems with dexterity, gait and balance [197,198]. Unlike Parkinson's disease, manganism is not associated with loss of smell and patients are typically unresponsive to treatment with L-DOAP [195]. Symptoms of late-stage manganism become more severe over time even if the source of exposure is removed and brain manganese levels return to normal [197].

Several recent studies attempt to examine the effects of chronic low-dose manganese overexposure on development in children. The earliest study of this kind was conducted in the Chinese province of Shanxi. Drinking water there had been contaminated through improper sewage irrigation and contained 240–350 $\mu\text{g Mn/L}$. Although WMn concentrations at or below 300 $\mu\text{g Mn/L}$ are considered safe by the US EPA and 400 $\mu\text{g Mn/L}$ are considered safe by the World Health Organization, the 92 children sampled (between 11 and 13 years of age) from this province displayed lower performance on tests of manual dexterity and rapidity, short-term memory, and visual identification when compared to children from an uncontaminated area. More recently, a study of 10-year-old children in Bangladesh showed a relationship between WMn concentration in well water and diminished IQ scores. A third study conducted in Quebec examined school children between the ages of 6 and 15 living in homes that received water from a well containing 610 $\mu\text{g Mn/L}$; controls lived in homes that received water from a 160 $\mu\text{g Mn/L}$ well. Children in the experimental group showed increased hyperactive and oppositional behaviors [192].

Chronic low-dose manganese intoxication is strongly implicated in a number of neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. It may also play a role in the development of multiple sclerosis, restless leg syndrome, and Huntington's disease. A protein called DMT1 is the major transporter involved in manganese absorption from the intestine, and may be the major transporter of manganese across the blood-brain barrier. DMT1 also transports inhaled manganese across the nasal epithelium. The putative mechanism of action is that manganese overexposure and/or dysregulation lead to oxidative stress, mitochondrial dysfunction, glutamate-mediated excitotoxicity, and aggregation of proteins.

2.12. Platinum

Platinum is a chemical element with the chemical symbol Pt and an atomic number of 78. Its name is derived from the Spanish term *platina*, which is literally translated into "little silver" [198,199]. It is a dense, malleable, ductile, precious, gray-white transition metal. Platinum is used in catalytic converters, laboratory equipment, electrical contacts and electrodes, platinum resistance thermometers, dentistry equipment, and jewelry. Because only a few hundred tons are produced annually, it is a scarce material, and is highly valuable and is a major precious metal commodity. Being a heavy metal, it leads to health issues upon exposure to its salts, but due to its corrosion resistance, it is not as toxic as some metals [200]. Compounds containing platinum, most notably cisplatin, are applied in chemotherapy against certain types of cancer [201].

In the laboratory, platinum wire is used for electrodes; platinum pans and supports are used in thermo gravimetric analysis because of the stringent requirements of chemical inertness upon heating to high temperatures (~1000 °C). Platinum is used as an alloying agent for various metal products, including fine wires, noncorrosive laboratory containers, medical instruments, dental prostheses, electrical contacts, and thermocouples. Platinum-cobalt, an alloy of roughly three parts platinum and one part cobalt, is used to make relatively strong permanent magnets [202, 203]. Platinum-based anodes are used in ships, pipelines, and steel piers [204]. According to the Centers for Disease Control and Prevention, short-term exposure to platinum salts may cause irritation of the eyes, nose, and throat, and long-term exposure may cause both respiratory and skin allergies. The current OSHA standard is 2 micrograms per cubic meter of air averaged over an 8-hour work shift [205].

Platinum-based antineoplastic agents are used in chemotherapy, and show good activity against some tumors. As platinum is a catalyst in the manufacture of the silicone rubber and gel components of several types of medical implants (breast implants, joint replacement prosthetics, artificial lumbar discs, vascular access ports, etc.), the possibility platinum could enter the body and cause adverse effects have merited study. The Food and Drug Administration and other institutions have reviewed the issue and found no evidence to suggest toxicity *in vivo* [206,207].

2.13. Potassium

Potassium is a chemical element with symbol K (from Neo-Latin *kalium*) and atomic number 19. Elemental potassium is a soft silvery-white alkali metal that oxidizes rapidly in air and is very reactive with water, generating sufficient heat to ignite the hydrogen emitted in the reaction and burning with a lilac flame.

Potassium ions are necessary for the function of all living cells. Potassium ion diffusion is a key mechanism in nerve transmission, and potassium depletion in animals, including humans, results in various cardiac dysfunctions. Potassium accumulates in plant cells, and thus fresh fruits and vegetables are a good dietary source of it. Conversely, most plants except specialist halophytes are intolerant of salt, and sodium is present in them only in low concentrations. This resulted in potassium first being isolated from potash, the ashes

of plants, giving the element its name. For the same reason, heavy crop production rapidly depletes soils of potassium, and agricultural fertilizers consume 95% of global potassium chemical production [208].

Potassium is the eighth or ninth most common element by mass (0.2%) in the human body, so that a 60 kg adult contains a total of about 120 g of potassium [209]. The body has about as much potassium as sulfur and chlorine, and only the major minerals calcium and phosphorus are more abundant [210].

Potassium cations are important in neuron (brain and nerve) function, and in influencing osmotic balance between cells and the interstitial fluid, with their distribution mediated in all animals (but not in all plants) by the so-called Na^+/K^+ ATPase pump [211]. This ion pump uses ATP to pump three sodium ions out of the cell and two potassium ions into the cell, thus creating an electrochemical gradient over the cell membrane. In addition, the highly selective potassium ion channels (which are tetramers) are crucial for the hyperpolarization, in for example neurons, after an action potential is fired. The most recently resolved potassium ion channel is KirBac3.1, which gives a total of five potassium ion channels (KcsA, KirBac1.1, KirBac3.1, KvAP, and MthK) with a determined structure [212]. All five are from prokaryotic species.

Potassium can be detected by taste because it triggers three of the five types of taste sensations, according to concentration. Dilute solutions of potassium ions taste sweet, allowing moderate concentrations in milk and juices, while higher concentrations become increasingly bitter/alkaline, and finally also salty to the taste. The combined bitterness and saltiness of high-potassium solutions makes high-dose potassium supplementation by liquid drinks a palatability challenge [213,214]. Potassium is also important in preventing muscle contraction and the sending of all nerve impulses in animals through action potentials. By nature of their electrostatic and chemical properties, K^+ ions are larger than Na^+ ions, and ion channels and pumps in cell membranes can distinguish between the two types of ions, actively pumping or passively allowing one of the two ions to pass, while blocking the other [215]. A shortage of potassium in body fluids may cause a potentially fatal condition known as hypokalemia, typically resulting from vomiting, diarrhea, and/or increased diuresis [216]. Deficiency symptoms include muscle weakness, paralytic ileus, ECG abnormalities, decreased reflex response and in severe cases respiratory paralysis, alkalosis and cardiac arrhythmia [217].

Potassium is an essential macro mineral in human nutrition; it is the major cation (positive ion) inside animal cells, and it is thus important in maintaining fluid and electrolyte balance in the body. Sodium makes up most of the cations of blood plasma at a reference range of about 145 mmol/L (3.345 g)(1 mmol/L=1mEq/L), and potassium makes up most of the cell fluid cations at about 150 mmol/L (4.8 g). Plasma is filtered through the glomerulus of the kidneys in enormous amounts, about 180 liters per day [218]. Thus 602 g of sodium and 33 g of potassium are filtered each day. All but the 1–10 g of sodium and the 1–4 g of potassium likely to be in the diet must be reabsorbed. Sodium must be reabsorbed in such a way as to keep the blood volume exactly right and the osmotic pressure correct; potassium must be reabsorbed in such a way as to keep serum concentration as close as possible to 4.8 mmol/L (about 0.190 g/L) [219]. Sodium pumps in the kidneys must always operate to conserve sodium. Potassium must

sometimes be conserved also, but, as the amount of potassium in the blood plasma is very small and the pool of potassium in the cells is about thirty times as large, the situation is not so critical for potassium. Since potassium is moved passively [220,221] in counter flow to sodium in response to an apparent (but not actual) Donnan equilibrium [222] the urine can never sink below the concentration of potassium in serum except sometimes by actively excreting water at the end of the processing. Potassium is secreted twice and reabsorbed three times before the urine reaches the collecting tubules [223]. At that point, it usually has about the same potassium concentration as plasma. At the end of the processing, potassium is secreted one more time if the serum levels are too high. If potassium were removed from the diet, there would remain a minimum obligatory kidney excretion of about 200 mg per day when the serum declines to 3.0–3.5 mmol/L in about one week [224] and can never be cut off completely, resulting in hypokalemia and even death [225].

The potassium moves passively through pores in the cell membrane. When ions move through pumps there is a gate in the pumps on either side of the cell membrane and only one gate can be open at once. As a result, approximately 100 ions are forced through per second. Pores have only one gate, and there is only one kind of ion that can stream through, at 10 million to 100 million ions per second [226]. The pores require calcium in order to open [225] although it is thought that the calcium works in reverse by blocking at least one of the pores [228]. Carbonyl groups inside the pore on the amino acids mimic the water hydration that takes place in water solution [229] by the nature of the electrostatic charges on four carbonyl groups inside the pore [230].

A potassium intake sufficient to support life can in general be guaranteed by eating a variety of foods. Clear cases of potassium deficiency (as defined by symptoms, signs and a below-normal blood level of the element) are rare in healthy individuals. Foods rich in potassium include parsley, dried apricots, dried milk, chocolate, various nuts (especially almonds and pistachios), potatoes, bamboo shoots, bananas, avocados, soybeans, and bran, although it is also present in sufficient quantities in most fruits, vegetables, meat and fish [231].

Epidemiological studies and studies in animals subject to hypertension indicate that diets high in potassium can reduce the risk of hypertension and possibly stroke (by a mechanism independent of blood pressure), and a potassium deficiency combined with an inadequate thiamine intake has produced heart disease in rats [232]. There is some debate regarding the optimal amount of dietary potassium. For example, the 2004 guidelines of the Institute of Medicine specify a DRI of 4,700 mg of potassium (100 mEq), though most Americans consume only half that amount per day, which would make them formally deficient as regards this particular recommendation [233, 234]. Likewise, in the European Union, in particular in Germany and Italy, insufficient potassium intake is somewhat common [235]. Italian researchers reported in a 2011 meta-analysis that a 1.64 g higher daily intake of potassium was associated with a 21% lower risk of stroke [234].

Supplements of potassium in medicine are most widely used in conjunction with loop diuretics and thiazides, classes of diuretics that rid the body of sodium and water, but have the side effect of also causing potassium loss in urine. A variety of medical and non-medical supplements are available. Potassium salts such as potassium chloride may be dissolved in water,

but the salty/bitter taste of high concentrations of potassium ion make palatable high concentration liquid supplements difficult to formulate [234]. Typical medical supplemental doses range from 10 mmol (400 mg, about equal to a cup of milk or 6 US flu oz (180 ml) of orange juice) to 20 mmol (800 mg) per dose. Potassium salts are also available in tablets or capsules, which for therapeutic purposes are formulated to allow potassium to leach slowly out of a matrix, as very high concentrations of potassium ion (which might occur next to a solid tablet of potassium chloride) can kill tissue, and cause injury to the gastric or intestinal mucosa. For this reason, law in the US to only 99 mg of potassium limits non-prescription supplement potassium pills.

Individuals suffering from kidney diseases may experience adverse health effects from consuming large quantities of dietary potassium. End stage renal failure patients undergoing therapy by renal dialysis must observe strict dietary limits on potassium intake, as the kidneys control potassium excretion, and buildup of blood concentrations of potassium (hyperkalemia) may trigger fatal cardiac arrhythmia.

2.14. Selenium

Selenium is a chemical element with symbol Se and atomic number 34. It is a nonmetal with properties that are intermediate between those of its periodic table column-adjacent chalcogen elements sulfur and tellurium. It rarely occurs in its elemental state in nature, or as pure ore compounds. Jons Jacob Berselius, who noted the similarity of the new element to the previously known tellurium, discovered selenium in 1817.

Selenium salts are toxic in large amounts, but trace amounts are necessary for cellular function in many organisms, including all animals. Selenium is a component of the antioxidant enzymes glutathione peroxidase and thioredoxin reductase (which indirectly reduce certain oxidized molecules in animals and some plants). It is also found in three deiodinase enzymes, which convert one thyroid hormone to another. Selenium requirements in plants differ by species, with some plants requiring relatively large amounts, and others apparently requiring none [237].

Although it is toxic in large doses, selenium is an essential micronutrient for animals. In plants, it occurs as a bystander mineral, sometimes in toxic proportions in forage (some plants may accumulate selenium as a defense against being eaten by animals, but other plants such as locoweed require selenium, and their growth indicates the presence of selenium in soil) [237]. Selenium is a component of the unusual amino acids selenocysteine and selenomethionine. In humans, selenium is a trace element nutrient that functions as cofactor for reduction of antioxidant enzymes, such as glutathione peroxidases [238] and certain forms of thioredoxin reductase found in animals and some plants (this enzyme occurs in all living organisms, but not all forms of it in plants require selenium).

The glutathione peroxidase family of enzymes (GSH-Px) catalyzes certain reactions that remove reactive oxygen species such as hydrogen peroxide and organic hydroperoxides.



Selenium also plays a role in the functioning of the thyroid gland and in every cell that uses thyroid hormone, by participating as a cofactor for the three of the four known types of thyroid hormone deiodinases, which activate and then deactivate various thyroid hormones and their metabolites: the iodothyronine deiodinases are the subfamily of deiodinase enzymes that use selenium as the otherwise rare amino acid selenocysteine. Only the deiodinase iodotyrosine, which works on the last breakdown products of thyroid hormone, does not use selenium [239].

Selenium may inhibit Hashimoto's disease, in which the body's own thyroid cells are attacked as alien. A reduction of 21% in antibodies was reported with the dietary intake of 0.2 mg of selenium [240]. Increased dietary selenium intakes reduce the effects of mercury toxicity [241] and it is now recognized that the molecular mechanism of mercury toxicity involves irreversible inhibition of selenoenzymes that are required to prevent and reverse oxidative damage in brain and endocrine tissues [242,243]. Dietary selenium comes from nuts, cereals, meat, mushrooms, fish, and eggs. Brazil nuts are the richest ordinary dietary source (though this is soil-dependent, since the Brazil nut does not require high levels of the element for its own needs). In descending order of concentration, high levels are also found in kidney, tuna, crab, and lobster [244,245].

The human body's content of selenium is believed to be in the 13–20 milligram range [246]. The substance loosely called selenium sulfide (approximate formula SeS_2) is the active ingredient in some anti-dandruff shampoos [247]. The selenium compound kills the scalp fungus *Malassezia*, which causes shedding of dry skin fragments. The ingredient is also used in body lotions to treat *Tinea versicolor* due to infection by a different species of *Malassezia* fungus [248].

Selenium may be measured in blood, plasma, serum or urine to monitor excessive environmental or occupational exposure, confirm a diagnosis of poisoning in hospitalized victims or to assist in a forensic investigation in a case of fatal over dosage. Some analytical techniques are capable of distinguishing organic from inorganic forms of the element. Both organic and inorganic forms of selenium are largely converted to monosaccharide conjugates (selenosugars) in the body prior to being eliminated in the urine. Cancer patients receiving daily oral doses of selenothionine may achieve very high plasma and urine selenium concentrations [249]. Selenium deficiency is rare in healthy, well-nourished individuals. It can occur in patients with severely compromised intestinal function, those undergoing total parenteral nutrition, and [250] in those of advanced age (over 90). Also, people dependent on food grown from selenium-deficient soil are at risk. Although New Zealand has low levels of selenium in its soil, adverse health effects have not been detected [251]. Selenium deficiency as defined by low (<60% of normal) selenoenzyme activity levels in brain and endocrine tissues only occurs when a low selenium status is linked with an additional stress, such as high exposures to mercury [252] or as a result of increased oxidant stress due to vitamin E deficiency [253].

There are interactions between selenium and other nutrients, such as iodine and vitamin E. The effect of selenium deficiency on health remains uncertain, particularly in relation to

Kashin-Beck disease [254]. Also, there are interactions between selenium and other minerals, such as zinc and copper, it seems that high doses of Se supplement to pregnant animal might disturb the Zn:Cu ratio which, in turn, leads to Zn reduction. It can be concluded that the Zn status should be monitored when high dose of Se is supplemented to pregnant animal. Further studies need to be done with higher levels of Se supplement to confirm these interactions [255].

In some regions (e.g. various regions within North America) where low available selenium levels in soil lead to low concentrations in dry matter of plants, Se deficiency in some animal species may occur unless dietary (or injected) selenium supplementation is done [256]. Ruminants are particularly susceptible. In general, absorption of dietary selenium is lower in ruminants than in non-ruminants, and is lower from forages than from grain [257]. Ruminants grazing certain forages, e.g. some white clover varieties containing cyanogenic glycosides, may have higher selenium requirements, [258] presumably because of cyanide from the aglycone released by glucosidase activity in the rumen [258] and inactivation of glutathione peroxidases due to absorbed cyanide's effect on the glutathione moiety [260]. Neonate ruminants at risk of WMD (white muscle disease) may be administered both selenium and vitamin E by injection; some of the WMD myopathies respond only to selenium, some only to vitamin E, and some to either [261]. A number of correlative epidemiological studies have implicated selenium deficiency (as measured by blood levels) in a number of serious or chronic diseases, such as cancer [259], diabetes [262], HIV/AIDS [263] and tuberculosis. In addition, selenium supplementation has been found to be a chemopreventive for some types of cancer in some types of rodents. However, in randomized, blinded, controlled prospective trials in humans, selenium supplementation has not succeeded in reducing the incidence of any disease, nor has a meta-analysis of such selenium supplementation studies detected a decrease in overall mortality [264].

2.15. Sodium

Sodium is a chemical element with the symbol Na (from Latin: *natrium*) and atomic number 11. It is a soft, silvery-white, highly reactive metal and is a member of the alkali metals; its only stable isotope is ^{23}Na . The free metal does not occur in nature, but instead must be prepared from its compounds; was first isolated by Humphry Davy in 1807 by the electrolysis of sodium hydroxide. Sodium is the sixth most abundant element in the Earth's crust, and exists in numerous minerals such as feldspars and rock salt. Many salts of sodium are highly water-soluble, and their sodium has been leached by the action of water so that chloride and sodium (NaCl) are the most common dissolved elements by weight in the Earth's bodies of oceanic water.

In humans, sodium is an essential nutrient that regulates blood volume, blood pressure, osmotic equilibrium and pH; the minimum physiological requirement for sodium is 500 milligrams per day [265]. Sodium chloride is the principal source of sodium in the diet, and is used as seasoning and preservative, such as for pickling and jerky; most of it comes from processed foods [266]. The DRI for sodium is 2.3 grams per day [266], but on average people in the United States consume 3.4 grams per day [267], the minimum amount that promotes hypertension [268]; this in turn causes 7.6 million premature deaths worldwide [269].

The renin-angiotensin system regulates the amount of fluids and sodium in the body. Reduction of blood pressure and sodium concentration in the kidney results in the production of renin, which in turn produces aldosterone and angiotensin, retaining sodium in the urine. Because of the increase in sodium concentration, the production of renin decreases, and the sodium concentration returns to normal [270]. Sodium is also important in neuron function and osmoregulation between cells and the extracellular fluid, their distribution mediated in all animals by Na^+/K^+ -ATPase [271]; hence, sodium is the most prominent cation in extracellular fluid [272].

In C4 plants, sodium is a micronutrient that aids in metabolism, specifically in regeneration of phosphoenolpyruvate and synthesis of chlorophyll [273]. In others, it substitutes for potassium in several roles, such as maintaining turgor pressure and aiding in the opening and closing of stomata [274]. Excess sodium in the soil limits the uptake of water due to decreased water potential, which may result in wilting; similar concentrations in the cytoplasm can lead to enzyme inhibition, which in turn causes necrosis and chlorosis [275]. To avoid these problems, plants developed mechanisms that limit sodium uptake by roots, store them in cell vacuoles, and control them over long distances [276]; excess sodium may also be stored in old plant tissue, limiting the damage to new growth.

2.16. Zinc

Zinc, in commerce also spelter, is a metallic chemical element; it has the symbol Zn and atomic number 30. It is the first element of group 12 of the periodic table. Zinc is, in some respects, chemically similar to magnesium, because its ion is of similar size and its only common oxidation state is +2. Zinc is the 24th most abundant element in the Earth's crust and has five stable isotopes. The most common zinc ore is sphalerite (zinc blende), a zinc sulfide mineral. The largest mineable amounts are found in Australia, Asia, and the United States. Zinc production includes froth flotation of the ore, roasting, and final extraction using electricity.

Zinc is an essential mineral of "exceptional biologic and public health importance" [277]. Zinc deficiency affects about two billion people in the developing world and is associated with many diseases [278]. In children it causes growth retardation, delayed sexual maturation, infection susceptibility, and diarrhea, contributing to the death of about 800,000 children worldwide per year [277]. Enzymes with a zinc atom in the reactive center are widespread in biochemistry, such as alcohol dehydrogenase in humans [279]. Consumption of excess zinc can cause ataxia, lethargy and copper deficiency.

Zinc is included in most single tablet over-the-counter daily vitamin and mineral supplements [280]. Preparations include zinc oxide, zinc acetate, and zinc gluconate [281]. It is believed to possess antioxidant properties, which may protect against accelerated aging of the skin and muscles of the body; studies differ as to its effectiveness [282]. Zinc also helps speed up the healing process after an injury [281]. It is also suspected of being beneficial to the body's immune system. Indeed, zinc deficiency may have effects on virtually all parts of the human immune system [282]. The efficacy of zinc compounds when used to reduce the duration or severity of cold symptoms is controversial [283]. A 2011 systemic review concludes that supplementation yields a mild decrease in duration and severity of cold symptoms [284].

Optimum dosing and formulation have not been determined. The studies included in the 2011 review used a variety of forms and doses of zinc, including zinc gluconate or zinc acetate lozenges and zinc sulfate syrup. The doses ranged from 30 to 160 milligrams per day. The researchers noted the following: *"Given the variability in the populations studied (no studies from low-or middle-income countries), dose, formulation and duration of zinc used in the included studies, more research is needed to address these variabilities and determine the optimal duration of treatment as well as the dosage and formulations of zinc that will produce clinical benefits without increasing adverse effects, before making a general recommendation for zinc in treatment of the common cold."*

Zinc serves as a simple, inexpensive, and critical tool for treating diarrheal episodes among children in the developing world. Zinc becomes depleted in the body during diarrhea, but recent studies suggest that replenishing zinc with a 10-to 14-day course of treatment can reduce the duration and severity of diarrheal episodes and may also prevent future episodes for up to three months [285]. The Age-Related Eye Disease Study determined that zinc could be part of an effective treatment for age-related macular degeneration [286]. Zinc supplementation is an effective treatment for acrodermatitis enteropathica, a genetic disorder affecting zinc absorption that was previously fatal to babies born with it [287]. Gastroenteritis is strongly attenuated by ingestion of zinc, and this effect could be due to direct antimicrobial action of the zinc ions in the gastrointestinal tract, or to the absorption of the zinc and re-release from immune cells (all granulocytes secrete zinc), or both [288,289]. In 2011, researchers at John Jay College of Criminal Justice reported that dietary zinc supplements could mask the presence of drugs in urine. Similar claims have been made in web forums on that topic [289].

Although not yet tested as a therapy in humans, a growing body of evidence indicates that zinc may preferentially kill prostate cancer cells. Because zinc naturally homes to the prostate and because the prostate is accessible with relatively non-invasive procedures, its potential as a chemotherapeutic agent in this type of cancer has shown promise [290]. However, other studies have demonstrated that chronic use of zinc supplements in excess of the recommended dosage may actually increase the chance of developing prostate cancer, also likely due to the natural buildup of this heavy metal in the prostate [291]. Topical zinc preparations include those used on the skin, often in the form of zinc oxide. Zinc preparations can protect against sunburn in the summer and windburn in the winter [292]. Applied thinly to a baby's diaper area (perineum) with each diaper change, it can protect against diaper rash [292]. Zinc lactate is used in toothpaste to prevent halitosis [138]. Zinc pyrithione is widely applied in shampoos because of its anti-dandruff function [293]. Zinc ions are effective antimicrobial agents even at low concentrations [294].

Zinc is an essential trace element, necessary for plants [295], animals [296], and microorganisms [297]. Zinc is found in nearly 100 specific enzymes [298], serves as structural ions in transcription factors and is stored and transferred in metallothioneins [299]. It is "typically the second most abundant transition metal in organisms" after iron and it is the only metal that appears in all enzyme classes [295]. In proteins, Zn ions are often coordinated to the amino acid side chains of aspartic acid, glutamic acid, cysteine and histidine. The theoretical and computational description of this zinc binding in proteins (as well as that of other transition metals) is difficult [300]. There are 2-4 grams of zinc [301] distributed throughout the human body. Most zinc is

in the brain, muscle, bones, kidney, and liver, with the highest concentrations in the prostate and parts of the eye [302]. Semen is particularly rich in zinc, which is a key factor in prostate gland function and reproductive organ growth [303].

In humans, zinc plays "ubiquitous biological roles"[275.] It interacts with a wide range of organic ligands [275], and has roles in the metabolism of RNA and DNA, signal transduction, and gene expression. It also regulates apoptosis. A 2006 study estimated that about 10% of human proteins (2800) potentially bind zinc, in addition to hundreds which transport and traffic zinc; a similar *in silico* study in the plant *Arabidopsis thaliana* found 2367 zinc-related proteins [293].

In the brain, zinc is stored in specific synaptic vesicles by glutamatergic neurons [304] and can modulate brain excitability [305]. It plays a key role in synaptic plasticity and so in learning [159]. However, it has been called the brain's dark horse [306] since it also can be a neurotoxin, suggesting zinc homeostasis plays a critical role in normal functioning of the brain and central nervous system [307]. Zinc deficiency is usually due to insufficient dietary intake, but can be associated with malabsorption, acrodermatitis enteropathica, chronic liver disease, chronic renal disease, sickle cell disease, diabetes, malignancy, and other chronic illnesses [4]. Symptoms of mild zinc deficiency are diverse [308]. Clinical outcomes include depressed growth, diarrhea, impotence and delayed sexual maturation, alopecia, eye and skin lesions, impaired appetite, altered cognition, impaired host defense properties, defects in carbohydrate utilization, and reproductive teratogenesis [305]. Mild zinc deficiency depresses immunity [306], although excessive zinc does also [299]. Animals with a diet deficient in zinc require twice as much food in order to attain the same weight gain as animals given sufficient zinc [309]. Groups at risk for zinc deficiency include the elderly, children in developing countries, and those with renal insufficiency. The zinc chelator phytate, found in seeds and cereal bran, can contribute to zinc malabsorption [278].

Despite some concerns [310], western vegetarians and vegans have not been found to suffer from overt zinc deficiencies any more than meat-eaters [311]. Major plant sources of zinc include cooked dried beans, sea vegetables, fortified cereals, soy foods, nuts, peas, and seeds [306]. However, phytates in many whole-grains and fiber in many foods may interfere with zinc absorption and marginal zinc intake has poorly understood effects. There is some evidence to suggest that more than the US RDA (15 mg) of zinc daily may be needed in those whose diet is high in phytates, such as some vegetarians [308]. These considerations must be balanced against the fact that there is a paucity of adequate zinc biomarkers, and the most widely used indicator, plasma zinc, has poor sensitivity and specificity [312]. Diagnosing zinc deficiency is a persistent challenge [277].

Nearly two billion people in the developing world are deficient in zinc [278]. In children it causes an increase in infection and diarrhea, contributing to the death of about 800,000 children worldwide per year [275]. The World Health Organization advocates zinc supplementation for severe malnutrition and diarrhea [313]. Zinc supplements help prevent disease and reduce mortality, especially among children with low birth weight or stunted growth [313]. However, zinc supplements should not be administered alone, since many in the developing world have several deficiencies, and zinc interacts with other micronutrients [314].

3. Halotherapy

Salt therapy, halotherapy or speleotherapy [315] is the use of salt mines, caves or other forms of exposure to salt air in the belief that this confers a health benefit. These natural deposits of mineral halite are derived from evaporated ancient lakes and seas. The unrefined rock salt, primarily sodium chloride, also includes varying concentrations of other mineral salts such as calcium and magnesium, manganese and sulfates, which have additional therapeutic properties depending on the source [316]. The special characteristics of the microclimate of a salt mine include stable air temperature, humidity and lack of airborne pollutants such as pollens, and are unique to each mine. At depth the air pressure is also significantly higher than above ground, which has been found to benefit sufferers of respiratory diseases in studies conducted at the Dead Sea, which is below sea level.

There are records of improvements in the breathing of miners in Roman and medieval times. Dr. Felix Boczkowski, a physician at the Polish salt mine at Wieliczka wrote in 1843 that the miners there did not suffer from lung diseases and his successor set up a spa based upon these observations [317]. Modern use of this therapy started in Germany when Dr. Karl Hermann Spannagel [318] noticed improvement in the health of his patients after they hid in the Kluterthöhle karst cave to escape heavy bombing. It is now practiced in places such as Bystrianska in Slovakia [319] Wieliczka in Poland [320], Solotvyno in Ukraine [320] and many other East European countries [321].

Halogenerators are used to simulate the salted atmosphere of salt mines. These highly developed machines crush rock salt into dry micrometer sized particles, ionize the particles, and release them into the air. Salt particles of sizes 0.1-2.5 micrometers are able to escape the natural defenses of the upper airways and travel deep into the lung to the level of the alveoli. Typically used in a small room with floors and walls lined with rock salt, known as artificial salt room.

Salt lamps are another method of salt therapy. A large crystal of natural salt is hollowed out and heated with a tealight or lightbulb. The crystals give off an attractive glow in various colors of pink, orange, red or purple according to the minerals present.

Special home saline therapy devices were developed with the scope of making salt therapy easily available at home, replicating the seashore or speleotherapy aerosol. Hand-held devices and ultrasonic salinizer, use rock salt to create the microscopic breathable particles of salt. The hand-held salt inhaler uses dry rock salt and can deliver the salt aerosol by breathing through the mouth and exhaling through the nose, offering 1-2 hours daily exposure. The ultrasonic salinizer uses saline solution [322] made with natural rock salt, to create the salt aerosol. These salt particles are released into the indoor air and freely breathed during the night, offering 7-8 hours daily exposure, especially for chronic respiratory diseases [323]. Breathing an aerosol of hypertonic salt water (3-7% NaCl) has been found effective as a treatment for the heavy build up of mucus typical of cystic fibrosis [323]. The benefits of this treatment were first noticed by sufferers in Australia who were exposed to the natural aerosol of ocean salt spray [323].

The use of saline solution delivered by a nebulizer to treat bronchiolitis in children has also been systematically reviewed. The conclusion was current evidence suggests nebulized 3% saline may significantly reduce the length of hospital stay and improve the clinical severity score in infants with acute viral bronchiolitis [323].

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