The elements of life

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Here we describe the function of essential elements in biology and discuss about various aspects of these elements in human life as well as in bacteria and plants. The article highlights the importance of 28 essential elements in life from both chemical and biological perspective and their role in enzyme functions and several other biological pathways. Although the journey through periodic table illustrates the specific functions of a few elements, there may be other elements whose functions in living systems are poorly understood. Many drug molecules and metal-complexes have been discovered in the recent past for diagnosis and therapeutic purpose, which also highlight the importance of metal ions and synergistic functions of elements in human and other organisms.

Keywords: Chemical elements, periodic table, trace elements, transition metals.

Introduction

THE human body contains around 60 detectable chemical elements, but only about 28 of these elements, known as essential elements, are believed to participate in the healthy functioning of the body[1]. Depending on the concentration and dosage, the elements show either beneficial or deleterious effects. Many elements which are essential for bacteria and plants are not necessarily essential for humans directly. Here, we describe the biological importance of these 28 essential elements by taking a journey through the periodic table and highlight the chemistry associated with each of these elements in biological systems. In the periodic table (Figure 1), the 11 elements coloured in green are known as bulk elements because of their high abundance in biological systems. These six elements (C, H, O, N, S and P) constitute around 98% of all atoms present in proteins, nucleic acids, carbohydrates and other biological molecules (Figure 2)[3]. Therefore, these six elements are called biogenic elements and they combine with each other to form molecules that are the building blocks of a body.

Biological bulk elements

Oxygen (O)

Oxygen is the most abundant element in the earth's crust by weight, which is vital for the respiration. In 2019, the Nobel Prize in Physiology or Medicine has been awarded to William G. Kaelin Jr, Peter J. Ratcliffe and Gregg L. Semenza for their discoveries of how cells sense O_2 availability and on the establishment of adaptive response of O_2 for the cellular metabolism and physiological function[4]. In the human body, more than half of the body mass is oxygen. In redox reactions, oxygen accepts the electrons, which lead to the production of ATP, the energy source for the cell function (Figure 4). Homeostasis of O_2 is crucial for the survival of all vertebrates.

For example, lack of oxygen (hypoxia) leads to the development of myocardial and cerebral complications. Excess supplies of oxygen in tissues and organs (hyperoxia) also have the deleterious effects such as production of reactive oxygen species (ROS: $O_2^{\cdot-}$, H_2O_2, $OH^{\cdot}$), which induce oxidative stress by disrupting the balance between oxidant and antioxidant[5]. This oxidative stress results in damage to biomolecules such as DNA, proteins and lipids, leading to various pathophysiological conditions such as cardiovascular disease, neurodegeneration, HIV activation, cancer and ageing[6].

Hydrogen (H)

The lightest element in the period table has a remarkable role in biology although it can only form one type of bond – single bond. Water, which makes up more than 70% of human body, contains hydrogen. The pH of the body fluids and tissues are tightly regulated by proton pump with the help of proton (H^+) and a decrease in the pH 7.4 indicates the sign of distress in the body. In blood, carbonic acid (H_2CO_3)/bicarbonate and amino acids control the pH by buffering[3,7]. The release of Fe^{3+} from iron transport protein transferrin is also regulated by H^+ ions concentration[8]. Several redox enzymes use cofactor such as NAD(P)H, FAD, FMN, etc. which can supply hydride H^- in the reduction step of enzymatic cycles (Figure 4). In bacterial, the hydrogenase enzyme can produce H_2 gas, which is used as a reductant by a wide range of bacteria for their survival[9].

Carbon (C)

The second most abundant element in human can form different types of chemical bonds (single, double and triple) with other carbon atoms and a wide range of elements to make a variety of chemical compounds. For example, the hydrocarbon chains in cell membranes,

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H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
Ka	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	#Ln	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	##An	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn	Nh	Fl	Mc	Lv	Ts	Og

#	La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
##	Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

Figure 1. Periodic table of the elements (based on the latest release of the periodic table by IUPAC. The elements highlighted in colour (green, red and blue) are essential or possibly essential elements in life.

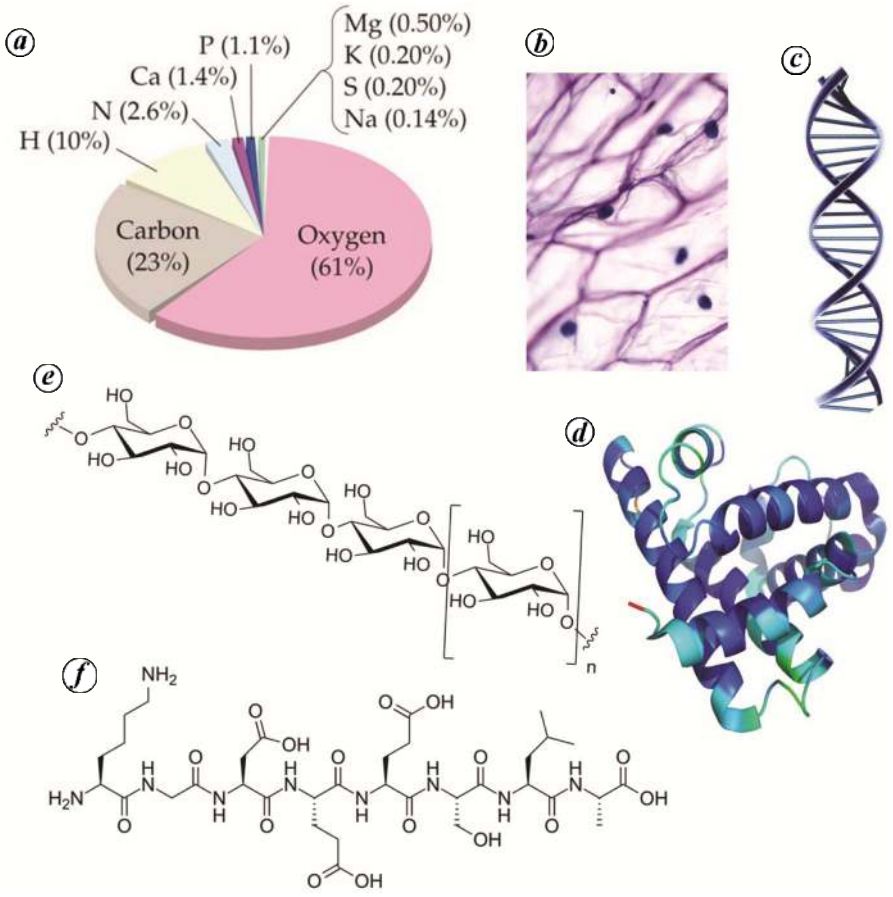

Figure 2. ***a***, Contribution (%) of bulk elements in human body. It indicates 98% of human body comprises C, H, O, N, S and P (www.pinterest.com); ***b***, ***c***, ***d***, Representative images of cell membrane, nuclic acids (DNA) and protein respectively; ***e***, Representative molecular structure of carbohydrates, major component of cell membrane; ***f***, Representative primary structure of proteins and peptide where amino acids are connected by peptide bonds.

amino acids, carbohydrates and nucleic acids predominantly comprise carbon. The structural components of most enzymes, organs and tissues are made of proteins and carbohydrates[3]. During photosynthesis, CO_2 combines with H_2O molecules to produce glucose ($C_6H_{12}O_6$) and O_2 which are the two essential components for the survival of life on earth (Figure 3). The gaseous molecule carbon monoxide (CO) produced from the breakdown of haem by haem oxygenase in a daily basis functions as signalling molecules in our body to combat infections[10].

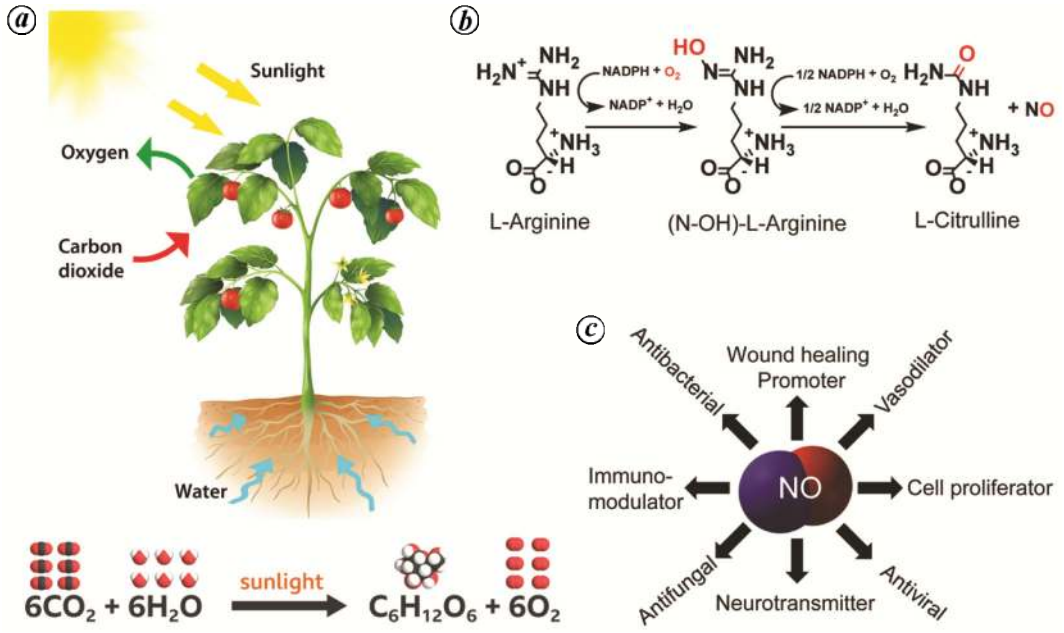

Figure 3. ***a***, Schematic representation of the production of glucose from CO_2 and H_2O by plants (https://photosynthesiseducation.com). ***b***, Conversion of arginine to citrulline by nitric oxide synthase (NOS) in presence of NADPH and O_2. The nitric oxide (NO) is generated in the process as by-products. ***c***, Various function of nitric oxide in our body.

Nitrogen (N)

More than 75% by volume of earth atmosphere consist of nitrogen gas. It gets incorporated in the biological cycle through N_2 fixation mechanism using nitrogenase family of enzymes (present in bacteria) that converts N_2 to NH_3. It has a wide range of oxidation states ranging from –3 (NH_3) to +5 (nitrate) and therefore, it is found in various biomolecules including amino acids, proteins and nucleobases. Proteins play key roles by catalysing essential biochemical reactions for the development of organs and tissues[3]. In recent past, scientists have discovered the role of nitric oxide (NO) as signalling molecules in the cardiovascular system[11]. Nitric oxide synthase (NOS) converts L-arginine to L-citrulline using NADPH and O_2 and thereby release NO in our body (Figure 3)[12]. Being a radical, NO is easily permeable to cell membrane and shows several other functions such as vasodilation, wound healing, cell proliferation, neurotransmission, anti-bacterial and anti-fungal (Figure 3)[13].

Sulphur (S)

It is found in most of the proteins in the form of two amino acids cysteine (Cys) and methionine (Met) that mediate major metabolic and catalytic activities. Sulphur undergoes reversible redox reactions to maintain the protein integrity, which is crucial for proper functioning of the protein[14]. Glutathione (GSH), the major intracellular tripeptide contains sulphur in the form of Cys amino acid (Figure 4). It acts as antioxidant to protect cells from oxidative damage and cofactor for one of the major cellular antioxidant enzymes glutathione peroxidase (GPx)[15]. Many other redox proteins and enzymes such as thioredoxin (Trx), thioredoxin reductase (TrxR), glutathione reductase (GR) and peroxiredoxin (Prx) also contain sulphur and participate in redox signalling[16]. The concentration of NO level in our body is also regulated by Cys thiols through the mechanism of protein nirosylation and denitrosylation[17]. In recent years, scientists have discovered the role of hydrogen sulphide (H_2S) as messenger molecule for the regulation of inflammation and endoplasmic reticulum stress signalling. Production of endogenous H_2S is beneficial for the prevention and treatment of atherosclerosis, the leading cause of cardiovascular morbidity and mortality. The two key enzymes, cystathionine β-synthase and cystathionine γ-lyase, produce H_2S from Cys or its derivatives[18]. Sulphur is also one of the major components in Fe/S cluster proteins such as Rieske proteins, ferredoxins and rubredoxins that participate in the electron transfer in biological systems[19].

Phosphorus (P)

In most of the living organisms, phosphorus is present in the structural framework of DNA and RNA as phosphodiester linkages. The cellular energy source ATP used by all the living organism is also a polyphosphate (Figure 4). The human body contains about 0.9 kg of phosphorus, 90% of which is present in apatite in bones and teeth and

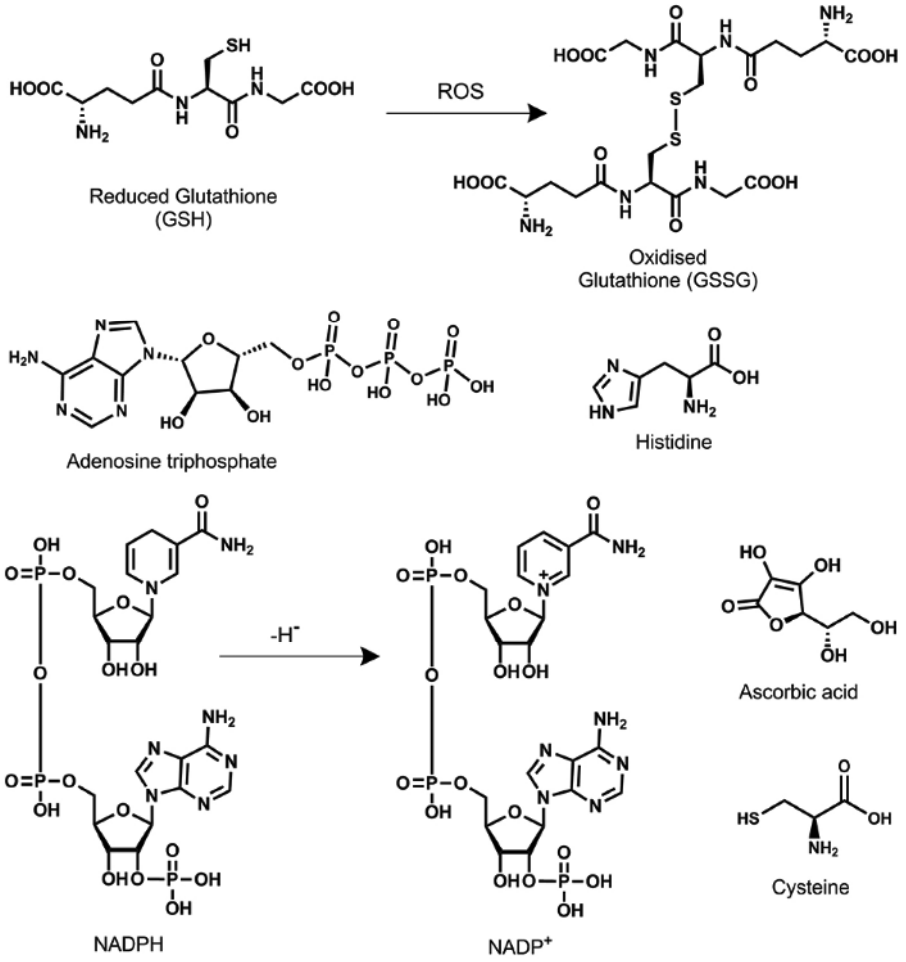

Figure 4. Representative molecular structures of some important biomolecules having C, H, O, N, S and P.

the rest in extracellular fluids and soft tissues[3,20]. A disruption in phosphorus homeostasis leads to many detrimental consequences such as cardiac failure, hemolysis, chronic kidney disease and respiratory failure[21].

Other bulk elements

Sodium and potassium both are essential in life and their biochemistry is similar although the ions (Na^+ and K^+) are distinguishable based on their ionic radii (1.02 versus 1.33 Å) and hydration enthalpies (–406 versus –322 kJ mol^{-1}). In the cell membranes, there are specific protein pumps for Na^+ and K^+ (Na/K ATPases) to maintain the concentration gradient of both the ions in plasma as well as intracellular matrix (Figure 5). This concentration gradient in turn helps for generating electrical potential gradient responsible for nerve impulses in our body[3,22].

Like Na and K, calcium (Ca) and magnesium (Mg) are also quite abundant elements in human body. Bones, skeletal muscles, teeth and soft tissues contain more than 95% of total Ca^{2+} and Mg^{2+} present in our body. Mg^{2+} present in extracellular fluids (1%) acts as essential cofactor to activate many enzymes and proteins which are involved in replication, transcription and translation processes[23]. The release of NO from nitric oxide synthase (NOS) is regulated by Ca^{2+} dependent calmodulin, which allows the electron transport from the C-terminal reductase domain of NOS to its haem containing N-terminal domain[24]. Both Ca^{2+} and Mg^{2+} are involved in the stabilization of lipid membranes, nucleic acids and in the regulation of skeletal and cardiac muscle contraction. The dysregulation of Mg and Ca can cause many disease conditions such as diabetes, gastrointestinal, coronary heart disease, osteoporosis and neurological manifestations[25].

Another essential element, chlorine (Cl) is widely distributed in the body and can exist in its oxidized form as well. The concentration of chloride ion in our blood (100 mM) and cellular compartments (25 mM in cytoplasm and 4 mM in nucleus) are regulated by membrane transport proteins for Cl^- ions[3,26]. Cystic fibrosis transmembrane conductance regulator (CFTR) controls the Cl^- ions transport and any mutations in the genes encoding CFTR can lead to a condition called cystic fibrosis[26]. Although hypochlorous acid (HOCl, oxidation state of Cl is +1) in higher dose is lethal to our body, myeloperoxidase in

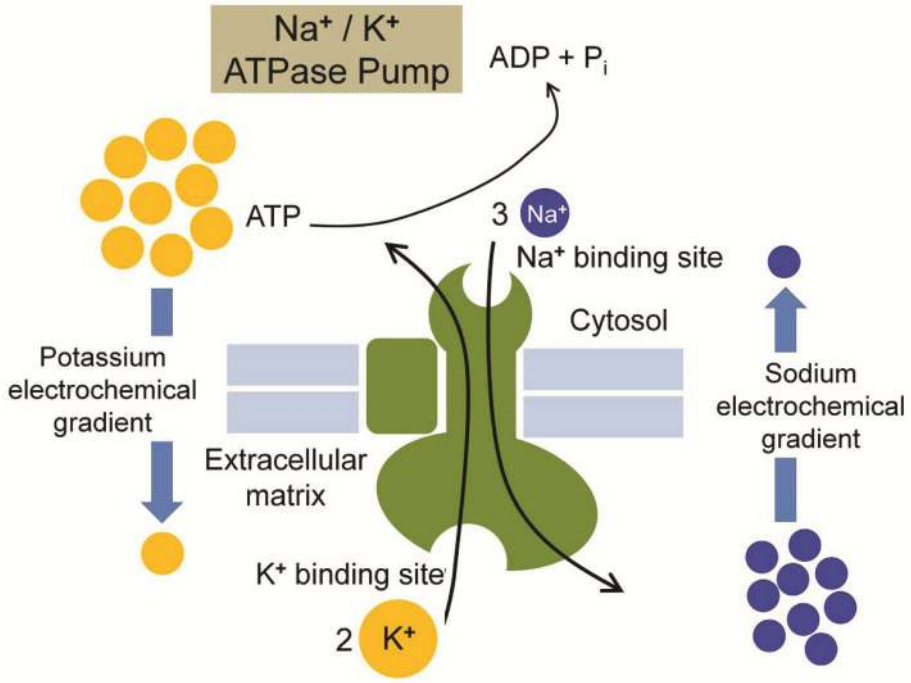

Figure 5. A schematic representation of the sodium/potassium protein pump in cell membrane. 3 Na^+ from cytosol go to the extracellular matrix and 2 K^+ ions from extracellular matrix come to cytosol and maintain the ions balance. The whole process is energy dependent and require the consumption of one molecule of ATP.

Table 1. Concentrations of transition metal ions in sea water and human plasma

Elements	Metal ions concentration ($\times 10^8$ M)		
	Sea water	Human plasma	Plasma/sea
Fe	0.005	2230	400,000
Zn	8	1720	215
Cu	1	1650	1650
Mo	10	1000	100
Co	0.7	0.0025	0.0035
Cr	0.4	5.5	13.75
V	4	17.7	4.4
Mn	0.7	10.9	15.6
Ni	0.5	4.4	8.8

Data is taken from reference 3d–h.

neutrophils (one type of white blood cells of our immune system) uses hydrogen peroxide (H_2O_2) and Cl^- to produce HOCl and eradicate all types of bacteria to protect our body[27].

Essential trace elements

The elements coloured in red in Figure 1 are essential trace elements mostly found in animals, plants and bacteria. Although these elements are required in small quantities, they play important roles in keeping the body working effectively. A careful observation of the data given in Table 1 suggests that the metal ion concentration in human plasma is much higher than that of sea water. This observation indicates that the biological systems possess efficient mechanisms for accumulation, storage and transport of these transition metals in higher organism and their special functions for the evolution of life in earth.

Transition metals

Iron (Fe)

The most abundant transition element in human is found in more than 500 proteins. Although human body contains 3–4 g of iron, only about 1 mg is lost per day, implying that the transport and storage of iron in biology is tightly regulated[28]. In oxygen environment, Fe is present in various oxidation states (+2, +3 and +4), where +3 is the most stable one and form highly insoluble hydroxides, leading to a decrease in the availability of soluble iron (salt of Fe^{2+}) in the surrounding medium for uptake. The deficiency of iron causes anaemia and ferrous sulphate ($FeSO_4$) was introduced in 1832 as a treatment of this deficiency in human[29]. Microorganisms find an alternate route for the uptake of iron through siderophores (Figure 6). Siderophores such as ferrichrome, enterobactin are cyclic compounds having hydroxamate, catecholate and carboxylate groups present to bind Fe^{3+} and they help in acquiring the required amount of iron from surrounding medium (Figure 6).

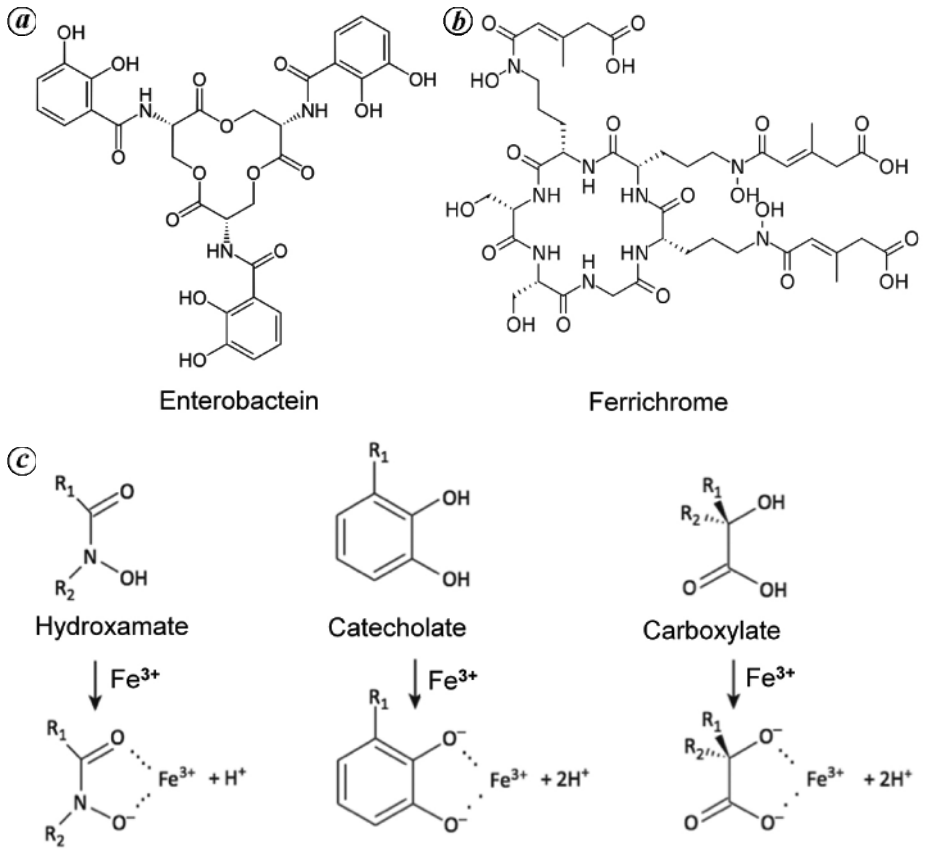

Figure 6. ***a***, ***b***, Two examples of well-known siderophores in bacteria; ***c***, Three different modes of binding of Fe^{3+} with siderophores for the transportation of iron inside microorganisms.

The binding constant for the Fe^{3+} complexes of ferrichrome and enterobactin are 10^{32} and 10^{40} respectively, which allow them to dissolve any Fe(III) compounds and take it inside the cells of microorganism, where the iron is released as Fe^{2+} (ref. 30). Plants use mugineic acid for the uptake of iron solubilizing $Fe(OH)_3$ in the pH range 4–9. Unlike bacteria, in multicellular organisms, most Fe(III) salts get dissolved to Fe^{3+} (aq) in the gastrointestinal tract or stomach at lower pH (1 or 2). Solubilized aqueous Fe(III) is sequestered in the intestinal wall by one specific protein called transferrin and transported to other cells[8,31]. Iron is released from transferrin when reduced to Fe(II) and is used immediately (for the synthesis of iron dependent metalloproteins and metalloenzymes such as haemoglobin, cytochrome p-450 and cytochrome *c*-oxidase, etc.) or stored by another protein named ferritin[32]. Ferritin stores iron in the form of Fe(III) effectively in a highly concentrated form and release in the form of Fe(II) (ascorbic acid reduce Fe(III) to Fe(II)) when required and thereby maintain the tight regulation of iron in the body (Figure 4).

As oxygen is much more soluble in nonpolar solvent than polar, a simple diffusion will not deliver O_2 fast enough to internal cells in multicellular organism. Therefore, in the case of vertebrates, 70% of total iron is used by red blood cells (RBCs) where O_2 binds with the Fe centre of haemoglobin and gets transported from lungs to cells. Another protein myoglobin is used to temporarily store O_2 in tissues[33]. The functional unit of myoglobin and haemoglobin contains a 5-coordinate iron centre where Fe is in +2 oxidation state (deoxygenated form), after oxygen binding Fe oxidation state changes to +3 and form six co-ordinate octahedral complexes (Figure 7).

Although both Mb and Hb have the same functional unit for oxygen binding, Hb shows cooperativity phenomenon for O_2 binding, whereas Mb does not exhibit such phenomenon, which helps to transfer O_2 from Hb to Mb (Figure 8)[33]. Unlike vertebrates, several other classes of invertebrates such as marine worms use non-haem iron, hemerythrin as O_2 storage and transport. It does not bind with O_2 in a cooperative manner (Figure 9).

Hemerythrin contains binuclear Fe^{2+} centre in its deoxygenated form (colourless) and upon oxygen binding, the oxidation state changes to Fe^{3+} (bright reddish violet) (Figure 9)[34]. Metalloenzymes cytochrome p-450 (CYPs) found in all kingdoms of life (animals, plants, fungi, archaea, protists, bacteria) contain haem-based Fe in their active site and they act as monooxygenase for the metabolism of drugs, synthesis of hormones and the

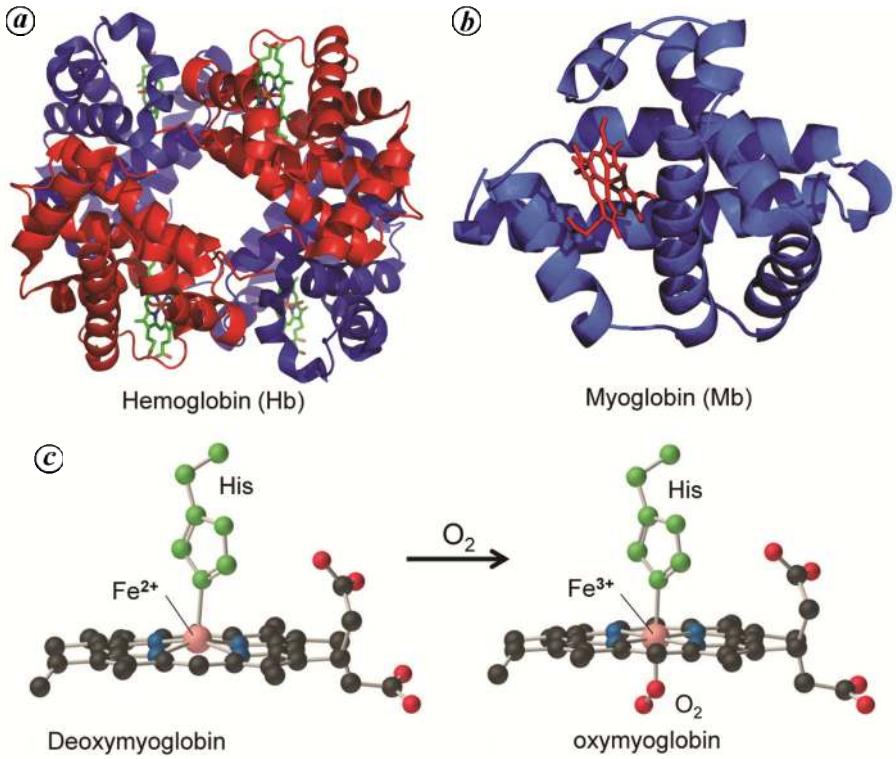

Figure 7. ***a***, ***b***, Structures of haemoglobin (Hb) and myoglobin (Mb). (Adapted from Richard Wheeler (Zephyris), 2007. Public domain Wikipedia. http://en.wikipedia.org/wiki/File: 1GZX_Haemoglobin.png.) Hb is a tetramer containing two subunits (α and β) whereas Mb is a monomer. In total Mb and Hb contain one and four Fe-haem in the active sites of protein respectively. The figures are reproduced from Wikipedia and reference 33a. ***c***, Oxygen binding of the penta-coordinate Fe(II) centre of myoglobin and formation of Fe(III)-octahedral complex (https://chem.libretexts.org/).

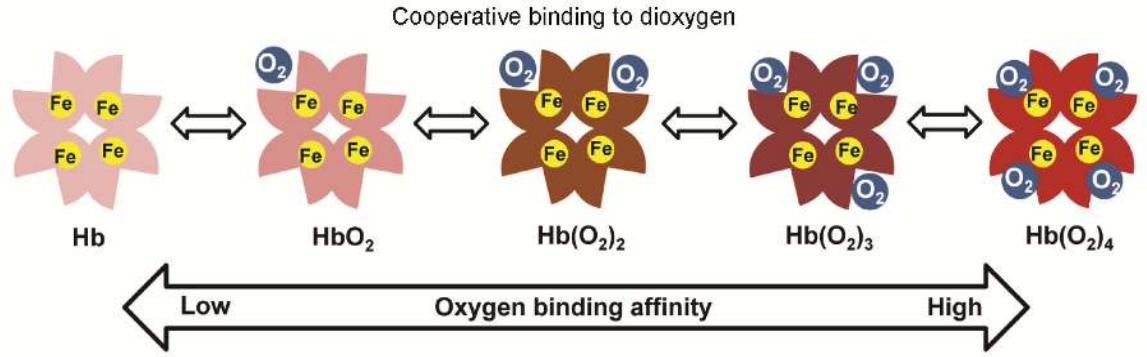

Figure 8. Cooperative binding of oxygen to haemoglobin. The figure indicates the binding of O_2 to Hb is stepwise where the binding of first oxygen molecule favours the second one to bind more strongly to Hb.

detoxification of xenobiotics as well[35]. Fe is also present in electron transfer chain, i.e. iron–sulphur cluster (Fe/S cluster) to transfer electron from the oxidized unit to the reduced unit and vice-versa in the redox reactions (Figure 10). The reversible changes in the oxidation state of Fe between +2 or +3 allow the quick transfer of electron in the required catalytic site (Figure 10)[19].

All cytochromes (*a*, *b*.*c*) and cytochrome *c*-oxidase (CcO), the terminal enzyme in the respiratory electron transport chain use haem-containing Fe in their active site. CcO converts O_2 molecules to water, where the Fe form ferryl oxo (Fe^{+4}=O) intermediate during the catalysis[36]. Hydrogenase and nitrogenase of bacterial enzymes also contain iron in their active core[8,37].

Zinc (Zn)

It is the 2nd most abundant transition metal in biology. In human, about 3000 Zn-containing proteins are known and

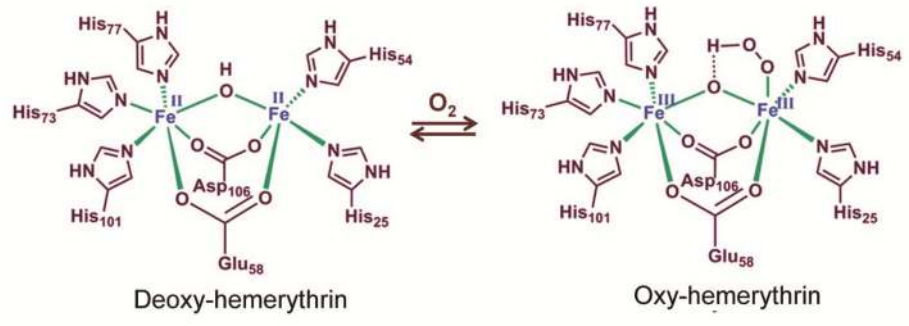

Figure 9. Active site structure of hemerythrin. In oxygenated form one of the iron centres in binuclear Fe(II) binds with dioxygen molecule in η^1 fashion and oxidation state of both the Fe centre change to Fe(III). The figure is reproduced from ref. 34b.

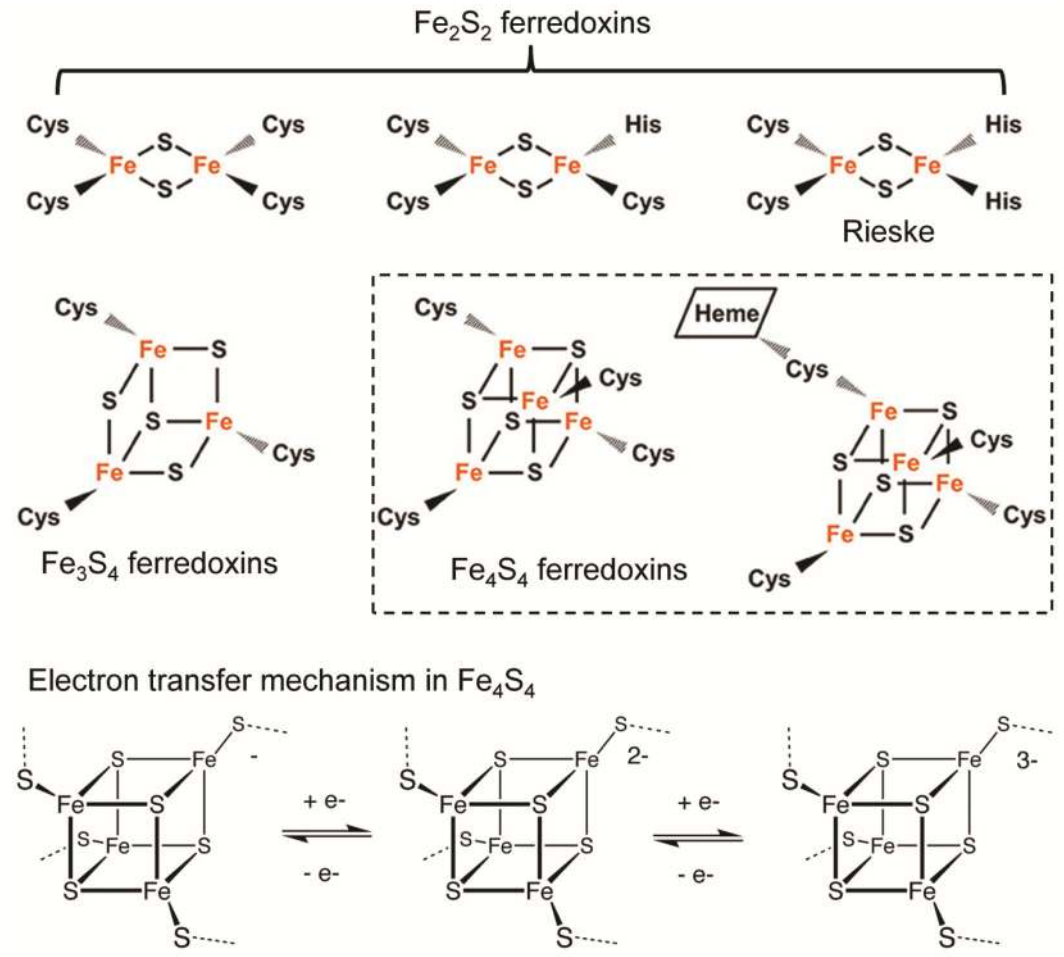

Figure 10. Active site structure of iron sulphur cluster and the electron transfer mechanism. The figures are reproduced from ref. 19b and www.wikiwand.com/en.

they play a key role for enzymatic catalysis as well as to give the structural stability of many other proteins[38]. Zn is redox inactive metal and exists in one oxidation state (+2), but it shows flexible coordination number (4 or 6) in biological environment, which favours the Zn metalloenzymes to catalyse chemical transformation. Hard bases such as O (Asp, Glu), N (His) as well as soft bases such as S (Cys) can bind with Zn^{2+} with equal preferences, which allows rapid exchange of ligands in Zn-metalloproteins. Carbonic anhydrase (CA) which maintains acid–base balance in blood and other tissues to help transport carbon dioxide out of tissues contains Zn in its active site. In lungs, CA converts bicarbonate to carbon dioxide, suited for exhalation (Figure 11)[39]. Alcohol dehydrogenase (an oxidoreductase) contains two independent Zn(II) centers; one oxidizes alcohol to aldehyde with the

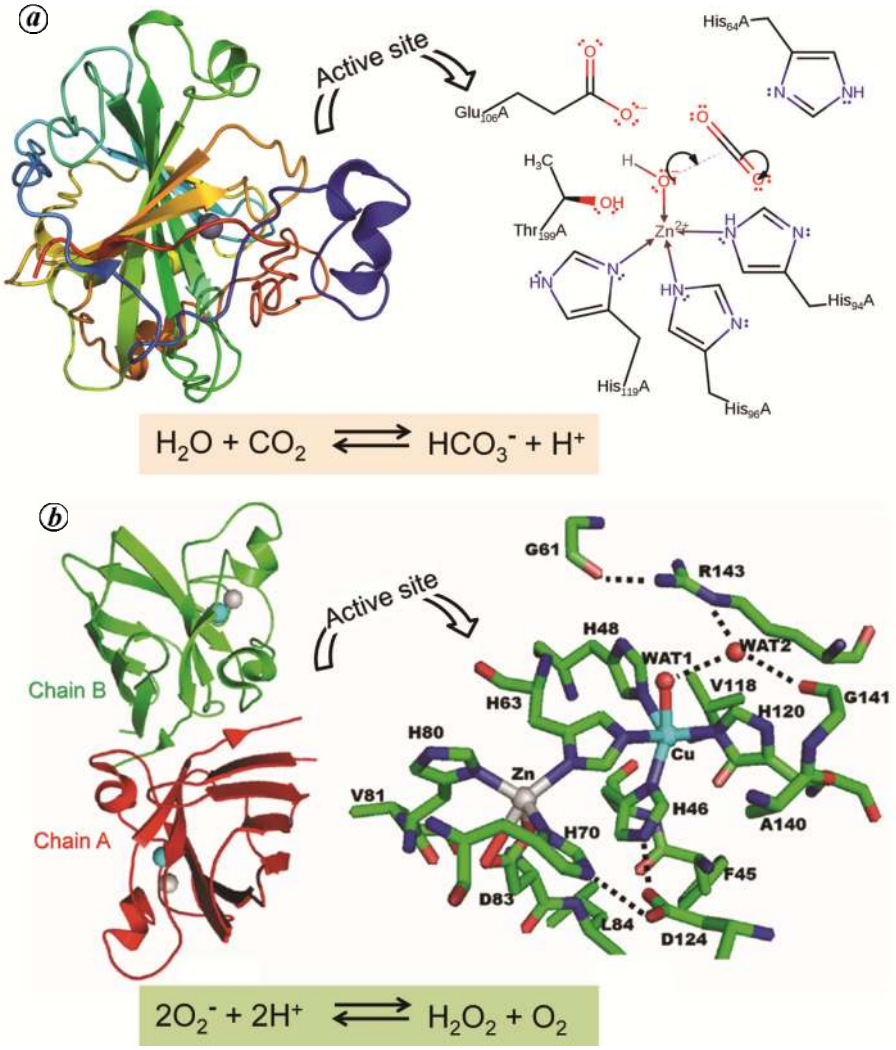

Figure 11. ***a***, Active site structure of carbonic anhydrase and the overall catalytic reaction. 3D X-ray of carbonic anhydrase II was obtained from PDB (Code ICA2). ***b***, Active site structure of CuZnSOD and its overall catalytic reaction. The figure is adopted and modified from ref. 42d.

help of NAD^+ to detoxify alcohol and other gives the structural stability of the enzyme[40]. Similar things are observed in the case of CuZn–superoxide dismutase (CuZn-SOD), where Cu catalyses the reduction of superoxide anion (O_2^-) and Zn centre is believed to give the structural stability of the enzyme (Figure 11)[41]. Bacteria evolve to counter the attack of antibiotics by developing class of Zn(II) hydrolases called as β-lactamases. They also have the enzyme phosphotriesterase (PTE) to detoxify pesticide organophosphate triester. Both the bacterial enzymes, β-lactamases and PTE, contain binuclear Zn(II) in their active sites to hydrolyse the respective substrates and thereby bacteria develop resistance in the environment[42].

Copper (Cu)

The third most abundant transition metal in biology maintains the proper functioning of organs and metabolic process. Human blood plasma contains ceruloplasmin, the major copper containing protein convert Fe(II) to Fe(III) and the patient lacking ceruloplasmin accumulate iron in their liver (aceruloplasminemia)[43]. Many metalloproteins and metalloenzymes (about 1% of total proteome present in eukaryotes and prokaryotes) contain Cu in their active sites and they are classified into three categories; type 1, type 2 and type 3. Type 1 Cu (blue copper protein) acts as electron transfer, whereas Cu in type 2 acts as a catalytic cites and binds directly to substrate[44]. Type 3 consists of binuclear Cu centre and found in oxygen transporting proteins (hemocyanin) and some oxidases (tyrosinase, cytochrome *c*-oxidase). Hemocyanin (found in mollusks and arthropods) binds with dioxygen reversibly for transport and storage of O_2. In the deoxygenated form, Cu present in +1 oxidation state and upon O_2 binding it shows dark blue colour because of change in oxidation state of Cu from +1 to +2 (Figure 12)[45]. Many fruits and vegetables such as apple, bananas and potatoes contain

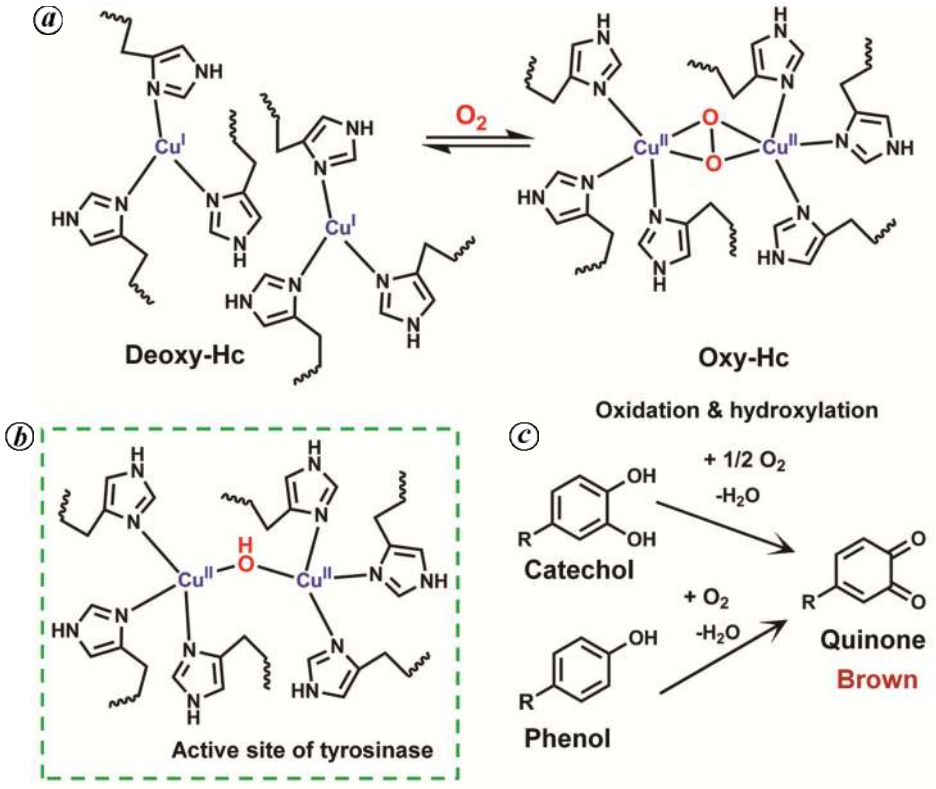

Figure 12. ***a***, Active site structure of hemocyanin and the binding of dioxygen. In deoxygenated form the oxidation state of both Cu ions are in +1 state and upon oxygen binding the oxidation states of both Cu changes to +2. ***b***, Active site structure of tyrosinase. ***c***, Oxidation and hydroxylation of catechol and phenolic compounds in presence of tyrosinase (oxidase enzymes), which form quinone derivatives responsible for the brown colouration in cut fruits and vegetables.

tyrosinase enzyme, which oxidizes catechol to quinone in presence of O_2 and turn brown when cut (Figure 12)[46]. Metalloenzymes such as CuZnSOD, Copper metallothionine (CuMT) modulate the reactive oxygen species (ROS) and oxidative stress level in our body (Figure 11)[41]. Homeostasis of Cu is crucial in human body as deficiency as well as excess of Cu leads to Menkes and Wilson's disease respectively, which lead to liver-failure, neuromodulation, respiration and angiogenesis[47].

Manganese (Mn)

Undoubtedly, Mn is an essential transition element in our body. There are many genes that code for Mn-enzymes which function in immune protection, metabolism, regulation of cellular energy and reproduction[3]. In biological systems, Mn exists mostly in +II and +III oxidation states and perpetuates the redox balance in cells especially in mitochondria with the help of Mn–SOD which reduces superoxide (O_2^-) to H_2O_2 and O_2 (ref. 48). Glutamine, the most abundant Mn-binding protein, is found in our brain cells (astrocytes). However, excessive Mn results in the production of ROS, alter mitochondrial ATP production, production of toxic metabolites and neurodegeneration such as Parkinson's disease[3,48,49]. In plant, the photosystem-II has a tetranuclear Mn^{IV}-complex which catalyses water oxidation and generate O_2 in the environment[50].

Vanadium (V)

After molybdenum, vanadium is the second most abundant transition element found in sea water with concentration of 35–50 nM and in marine organisms such as macroalgae, fungi and bacteria the concentration of vanadium is even higher (100 mg/kg)[51]. The most fascinating characteristic of vanadium is its various oxidation states and it exists in the form of oxyanion at neutral pH, which is an oxidizing agent that is structurally and electronically similar to phosphate. Interestingly, acid phosphatase enzymes, which use phosphate as cofactor, have evolved to be able to accommodate vanadate as a redox cofactor[52]. In vertebrates, particularly humans, V^{IV} and V^{V} species are likely to predominate and many vanadium complexes are in clinical trials as antidiabetic agents. To date, two classes of vanadium-containing enzymes have been identified in bacteria: vanadium nitrogenases and vanadium-dependent halo peroxidases (V-HPOs). The

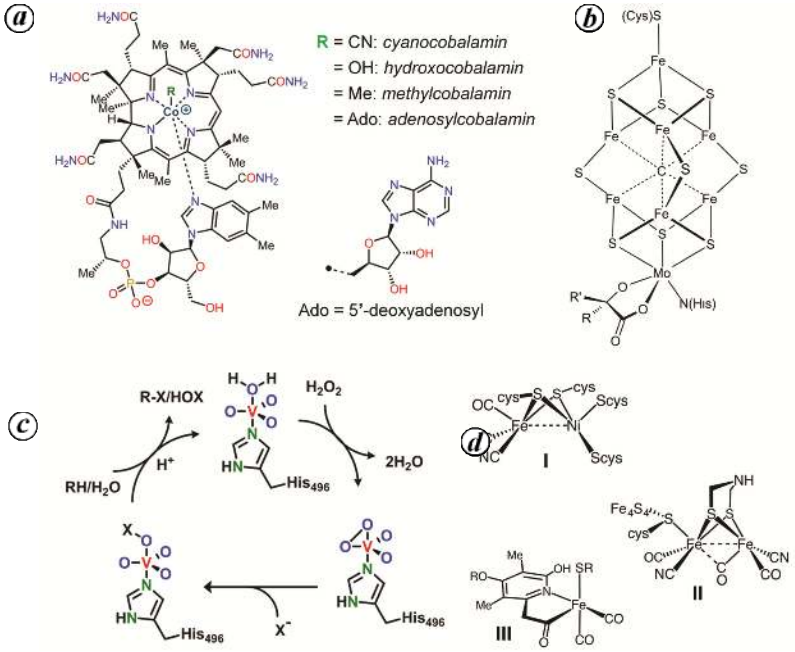

Figure 13. ***a***, Chemical structures of Vitamin-B_{12}. ***b***, Active site structure of nitrogenase which convert N_2 to ammonia (NH_3) and helps for nitrogen fixation. ***c***, Active site structure of V-halo peroxidase enzymes and the catalytic mechanism associated with the enzymes. ***d***, Three different active site structures of bacterial hydrogenase. The enzymes convert H_2 to H^+ and vice- versa. (Source: Wikipedia).

major function of V-HPOs is to incorporate halogen atoms into organic molecules (Figure 13)[37,53]. The blood of some species of ascidians and tunicates, also known as sea squirts and sea cucumbers, contains proteins called vanabins where V^{III} presents in much higher concentration (~350 mM)[54].

Cobalt (Co)

It is mostly found in vitamin B_{12}, also known as cobalamin (Figure 13). It acts a cofactor in DNA synthesis and plays a vital role in the metabolism of amino acids and fatty acids[55]. Microorganisms (bacteria and archaea) can only synthesize vitamin B_{12}, and for human, the daily recommended intake of vitamin B_{12} is 2–3 µg. In biological environment, Co present in various oxidation states (I, II and III) show the activity. The deficiency of vitamin B_{12} causes the accumulation of homocysteine in the body which is linked with cardiovascular, Alzheimer's diseases and chronic fatigue syndrome.

Nickel (Ni)

Ni is also an essential element for bacteria, but it is not clear whether it is essential for human or not. In microorganism, hydrogenase enzyme contains [NiFe] core in their active site to catalyse the conversion of H^+ to H_2 and vice-versa (Figure 13)[9].

Molybdenum (Mo)

From second and third transition metals series, Mo is the only essential trace element and it is taken up by cells in its oxyanion molybdate, $[Mo^{VI}O_4]^{2-}$ (ref. 56). Human genome codes four Mo enzymes where Mo is present as a cofactor, molybdopterin (MoCo) in xanthine oxidoreductase and sulphite oxidase family[57]. The deficiency of MoCo biosynthesis leads to the deficiency of these four Mo-enzymes activities, which cause rapid neurodegeneration and early childhood death[56,57]. In bacteria, nitrogenase enzyme, catalyses the conversion of N_2 to NH_3 contain Mo in its active site (Figure 13)[37].

Chromium (Cr)

It is the most controversial transition metal in terms of its toxicity and nutritional value. Although there is no gene that encodes for Cr-containing protein in human, dietary supplementation of Cr(III) complexes enhance the action of insulin in controlling normal levels of blood sugar[3,58]. In biology, chromium complexes show chameleon nature as Cr(III) is nontoxic whereas Cr(IV) is extremely toxic resulting in oxidative damage to DNA.

Main group elements

Selenium (Se), which is a prerequisite for the synthesis of selenocysteine (Sec), the 21st essential amino acid, was

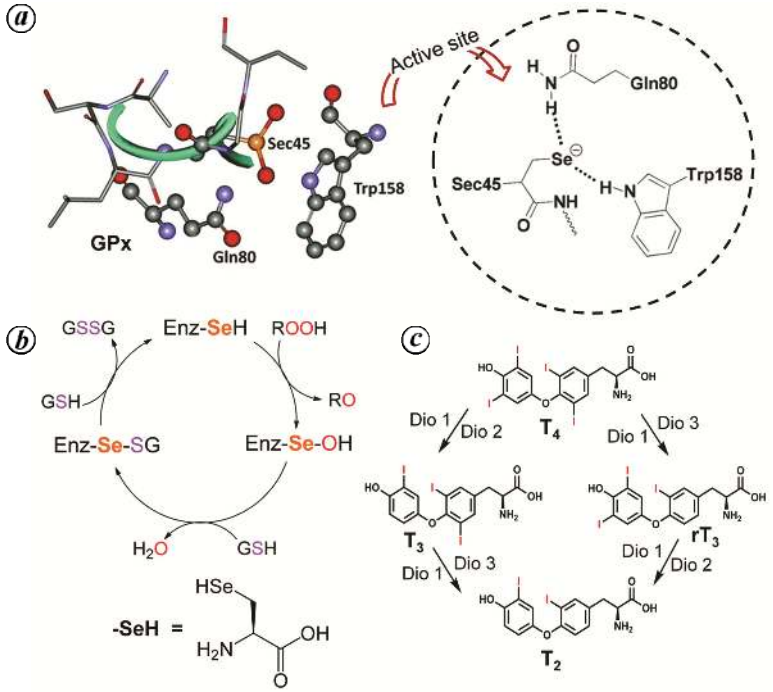

Figure 14. ***a***, (Left): Active site structure of glutathione peroxidase (GPx) enzyme in seleninic acid form determined by X-ray crystallography (PDB code 1GP1). (Right): Catalytic triad at the active site of GPx, where Se is present in the form of selenocysteine. The figures are reproduced from ref. 60f. ***b***, Catalytic cycle of GPx enzyme. The enzyme reduces hydrogen peroxides as well as lipid peroxides in presence of thiol cofactors especially GSH. ***c***, Chemical structures of thyroid hormones and the conversion of T_4 to T_3 in presence of iodothyronine deiodinases (Dio 1 and Dio 2).

believed to be toxic element in biology until Schwarz and Foltz identified it as a micronutrient for bacteria, mammals and birds[59]. Selenium biochemistry emerged in 1973 when two bacterial enzymes were reported to contain selenium. In the recent past, many enzymes such as glutathione peroxidases (GPxs), iodothyronine deiodinase (ID), thioredoxin reductase (TrxR), selenophosphatesynthetase were classified in eukaryotes[60]. GPx and TrxR act as major cellular antioxidants to combat against ROS such as hydroperoxides, peroxynitrite and lipid peroxides and control the redox signalling (Figure 14). Iodothyronine deiodinase plays an important role in the regulation of thyroid hormones in our body (Figure 14)[61]. Selenoproteins and enzymes contain selenocysteine (Sec) in their active site. UGA, commonly known as termination codon in mRNA translation for non-selenoprotein genes, encodes Sec which results in the synthesis of 25 selenoproteins involving respective functioning of our body[62]. Selenium along with iodine deficiency causes Kashin-Beck disease which leads to myocardial necrosis and weakening of the heart[63].

Iodine (I)

Although a healthy human body contains 16 mg iodine (I), it is essential for the growth and development of thyroid gland. Thyroid peroxidase synthesizes thyroid hormones especially thyroxine (T4) from iodide and tyrosine from the protein thyroglobulin[64]. Although, a small amount of 3,3′,5-triiodothyronine (T3), the active hormone of thyroid gland, is also produced during synthesis, most of the T3 is generated by deiodination of T4 by iodothyronine deiodinases (ID-1 and ID-2) (Figure 14)[65]. Iodine deficiency causes thyroid gland problems including goiter (Derbyshire neck), avoided by supplementation of iodized salt (NaCl with $KI/KIO_3/NaI/NaIO_3$ depending on the producer). Iodine also plays an essential role in metamorphosis, the process by which immature insect or amphibian transform to their adult stage[66].

Fluorine (F)

It is found at significant levels (3 g) in human and has beneficial effect on teeth and bones[67]. Fluoride (F^-) is a hard base and can replace OH^- in hydroxyapatite ($Ca_5(PO_4)_3OH$), the main constituent of bones and teeth to form fluorapatite ($Ca_5(PO_4)_3F$) (ref. 67). The small amount of fluoride (30 μM) is recommended to humans which is necessary to strengthen enamel but higher dose of fluorine can cause dental fluorosis.

Elements possibly essential for some organisms

Five elements in the periodic table highlighted in blue (Figure 1) have some beneficial effect in our body. Supplementation of strontium salts in toothpaste additives

show the advantages in the prevention of carcinogenesis and strengthens the enamel of teeth[68]. Strontium-89, a radionuclide was approved for the treatment of breast and metastatic prostate cancer where the chloride salt of Sr is administered to the patient[69]. Barium (Ba) is known in medicine for X-ray imaging of various parts of our body (gastrointestinal tract) including organs (stomach, duodenum, etc.) where relatively insoluble $BaSO_4$ meals is administered as radiopaque contrast agent[70]. There is no tungsten (W)-containing protein known in human till now. Some bacterial oxidoreductase enzymes use W instead of Mo in the active site of enzymes. In recent years, scientists have shown the application of polyoxotungstates in medicinal field such as antiviral, antibacterial and anti-cancer agents[71]. Arsenic (As) is known for its poisonous effect in humans and cause serious health problems[72]. Arsenite methyltransferase can take care of the low level of arsenic by converting it to mono/di-methyl-arsenic species and excrete rapidly through urine. As(III) has high affinity towards thiols and inhibit pyruvate dehydrogenase which results in decrease of ATP levels in cytoplasm in cells[73]. Bromine (Br) is also an essential trace element for life. Eosinophil peroxidase, found in immune cells of human and mammals, catalyses the generation of hypohalous acids specially HOBr, which plays a necessary role in post-translational modification of proteins for tissue development[74]. Further research is needed for better understanding of the essentiality of these five elements.

Summary and outlook

In summary, this review briefly describes the function of essential elements in biology with an emphasis on various aspects of trace elements in biological systems including human, bacteria and plants. As the importance of metals in medicine was realized 2000 years ago, many drug molecules and metal-complexes have been discovered in the recent past for diagnosis and therapy, but still the field is in its infancy as compared to organic molecules. Although some specific roles of essential elements are discussed in this review, these elements may play key roles in several other functions in living systems. The information about the complex pathways of biological processes where various elements of the periodic table play important roles will help in understanding various diseases and treatment options.

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