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Importance of Some Transition Metals and their Biological Role: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Transition Metal Chemistry is an international journal which deals with all aspects of the preparation of transition metal-based molecular compounds as well as including their physical, structural, kinetic, catalytic and biological properties, and their use in chemical synthesis as well as their application in the widest context, their role in naturally occurring systems and more.

Keywords: Transition metal; metal based compound; biological role etc.

1. INTRODUCTION

Metal coordination complexes have a wide variety of technological and industrial application ranging from catalysis to anticancer drugs. In these compounds the metal atom itself may have a number of roles, based on its coordination geometry, oxidation state and magnetic electronic and photochemical behaviours. The coordination chemistry of any transition metal seems to be a complicated function that involves numerous variables. Schiff bases are an important class of ligands in coordination chemistry and their complexing ability containing different donor atoms are widely reported [1-5] Medicinal inorganic chemistry as a discipline is

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considered to have boosted with the discovery of the anticancer properties of cisplatin. Thus the application of inorganic chemistry to medicine is a rapidly developing field, and novel therapeutic and diagnostic metal complexes are now having an impact on medicinal practice.[6-8].There are significant structural differences between ruthenium and platinum-based antitumor drugs; yet ruthenium based drugs could be suitable alternatives to cis-platin and carbo-platin.[9-10]. With the new emerging fields of science viz.; genetic engineering molecular biology, cell biology, nano science, biotechnology, magnetic resonance imaging bioinformatics etc. The intellectual ability of the chemist plays a pivotal role in the development of new bioactive molecules. The primary task of the chemist is to prepare specific new molecules that can lead more efficiently to useful drug discovery. The preparation of a new ligand was perhaps the most important step in the development of metal complexes which exhibit unique properties and novel reactivity. Since the electron donor and electron acceptor properties of the ligand, structural function groups and the position of the ligand in the coordination sphere together with the reactivity of coordination compounds may be the factor for different studies [11-13]. Their interest stems from the ease with which they can be synthesized, due to their versatility and wide range of complexing ability. Owing to large variety of coordination geometries, coordination number and modes of interaction with their ligands, metal complexes give access to different field of pathways in cancer treatment than do organic compounds. The discovery of the anticancer properties of cisplatin in the 1960s was a breakthrough event as far as interest in metal complexes was concerned.[14-15] Since then a tremendous number of novel metal complexes have been synthesized and evaluated to find species with better antimicrobial properties, lower toxic side effects, and less microbial resistance to cisplatin [16-23]. The metal complexes of transition element with heterocyclic ligands, especially those containing nitrogen and sulphur have diverse applications in various fields including biology and antiherbicidal activities of thioamide ligands and its metal complexes are well known and get more attraction recently. Sulphur and nitrogen donor ligands are also used as powerful pesticides. The well documented biological activities of heterocyclic ligands as well as their metal complexes have attracted much attention over the years. A numbers of heterocyclic compounds are well known and such activities have often been related to their chelating abilities towards one more essential trace metal ions. Being fascinated by significant biological implications of transition metal complexes of various Schiff bases.

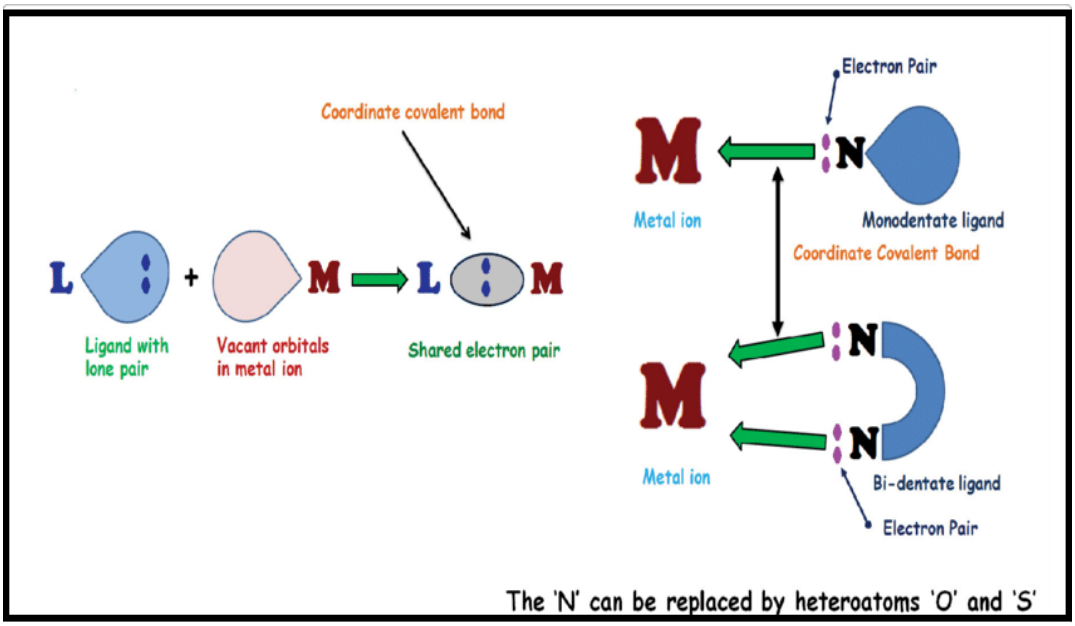

Fig. 1. Diagrammatic representation of the coordination complex

2. METHODS

2.1 Schiff Base Complexes Used as Drugs

Schiff base complexes have remained an important and popular area of research due to their simple synthesis, versatility and diverse range of applications. The Schiff base transition metal complexes have been extensively studied in recent years owing to their pharmacological properties. Substantial cytotoxic effects of transition metal complexes containing Schiff base were examined on several neuronal cell lines. It is well known fact that N, S and O donor atoms play a prominent key role in the coordination of metal at the activity sites of neumerous metallobiomolecules. Many investigations have proved that binding of drugs to a metallo-element enhances its activity and in some cases complex possess even more healing properties than the parent drugs. Metal complexes offer a platform for the design of noval therapeutic compounds. Taking into account the highly desirable attributes of this type of ligands vast families of bidentate, tetradentate Schiff base ligated complexes, of wide applicability as catalysts in numerous organic reactions, have been studied.

3. SCOPE OF THE PRESENT INVESTIGATIONS

Schiff bases of a large class of organic compound containing the azomethine group (HC=N), many chemotherapeutically important sulpha drugs like sulphadiazine, sulphamerazine etc. The metal complexes derived from sulpha drug and many of their complexes exhibit a wide range of biological activity. Several reports on Schiff base complexes of metal derived from sulpha drugs. The condensation product of sulphadiazine with aldehydes its derivatives gives biological activity increases with complexation. The Schiff base and their metal complexes having wide range of biological property. The Schiff base metal complexes show more antibacterial, antifungal and antiviral activity than the individual Schiff base. The reactivity, specificity and a number of applications in industry, agriculture and medicine, continue to provide the necessary impetus to the study of Schiff base complexes with transition and inner transition metals. In the present context a brief relevant survey of literature on Schiff base ligand and their metal complexes showed that more work on some mixed ligand complexes to be done, even complexes are available in the literature. In view of the above facts it was considered worthwhile to synthesize a variety of mixed ligand Schiff base metal complexes.

4. CLASSES OF METAL BASED PHARMACEUTICALS

There are various classes of metal based pharmaceuticals that can be divided into seven groups depending on which part of the structure is responsible for the biological activity of the compound.

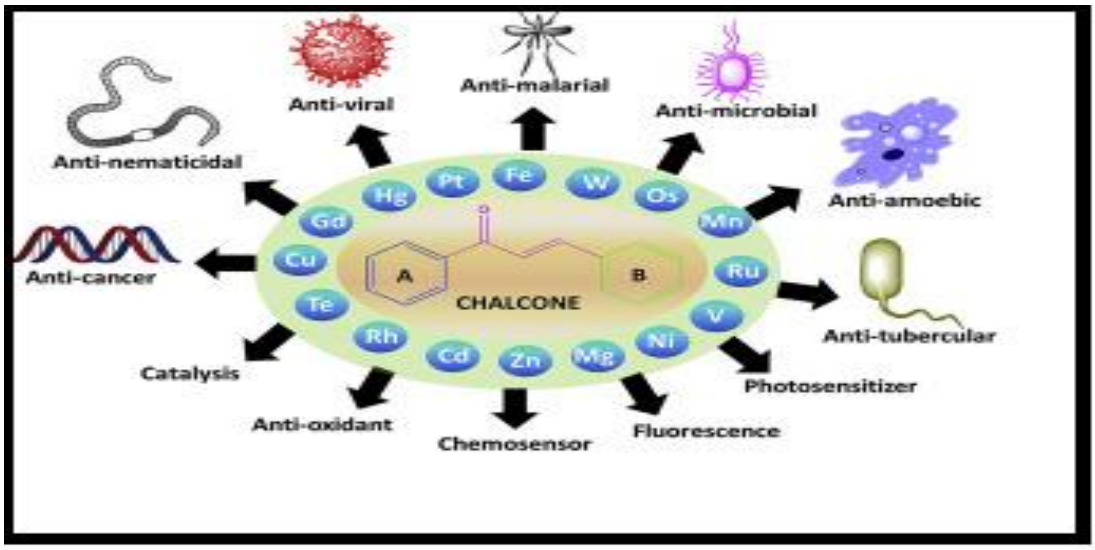

Fig. 2. Schiff Base complex used in various drug category

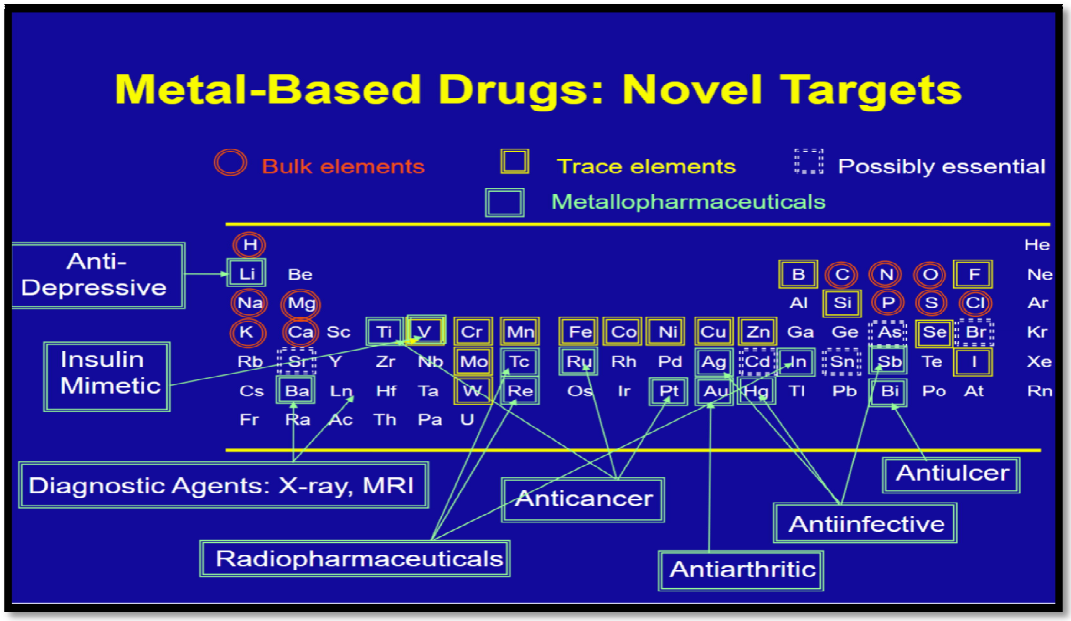

Fig.3. Diagram represents the metal based pharmaceuticals

a. Entire inert complex is active

Here the complexes are synthesized from smaller and simpler components. An example is the group of ruthenium complexes that are highly potent inhibitors of protein kinases [16].

b. Entire reactive complex is active

The copper complexes of NSAIDs that can mimic the actions of some enzymes, for instance superoxide dismutase, and have an analgesic effect. Very active complexes are the macrocyclic [17] and porphyrin [18] Mn(II) complexes. A five-coordinate intermediate is probably involved in the mechanism of action of the macrocylic complex.

c. A fragment of the complex is active

These are of special importance because the non-leaving ligands can mediate the interaction with the target and give selective activity. Platinum(II) complexes such as cisplatin are representatives of this group because they lose the anionic ligands (i.e., chloride) and form coordinate bonds with DNA. (To be discussed in detail below.) However, their toxic side effects have been a problem and require development of new less toxic prodrugs in form of platinum(IV) complexes [19]. Yet, another use of platinum(IV)complexes is their activation on exposure to light [20].

5. THE METAL ION OR ONE OF ITS BIOTRANSFORMATION PRODUCTS IS ACTIVE

The complexes that deliver an active metal are for instance insulin potentiating vanadium complexes. Orthovanadate mimics phosphate and inhibits the protein tyrosine phosphatases causing an increased cellular uptake of insulin [21]. However, the problem is with the bioavailability from the gastric system. One of the maltolato complexes ofvanadium(IV), bis(ethylmaltolato)oxovanadium (IV), appeared to be effective and entered phase I of the human trials with no adverse effects [22]. One of the least toxic transition metals it is unfortunately taken up and stored in bones, resulting in side effects.

6. ONE OR MORE OF THE LIGANDS ARE RESPONSIBLE FOR THE ACTIVITY

The complexes serve as prodrugs and the metal ions play a passive role, delivering an active ligand tothe target and keeping it away from the sites where they show toxicity. There are NO releasing and scavenging complexes reported effective in animal models [24]. On the other hand, CO releasing molecules showed promising positive inotropic effect on insolated rat hearts [25]. As tumor hypoxia presents a basis for the

selective targeting of solid tumours, cobalt(III) complexes have been tested as potential hypoxiaactivated prodrugs [26]. Moreover, copper(II) complexes of NSAID drugs in comparison to free agents cause less gastric and small intestinal damage [27].

7. ANTIINFECTIVE METAL ION COMPLEXES

Another therapeutical challenge in medicine apart from pharmaceuticals active against cancer is antiinfective therapy. There are many substances active against bacteria, fungi or viruses, however, even the best antibiotics can be ineffective at treating diseases because of ever increasing drug resistance. Therefore, much effort is directed at treating bacterial infections with compounds of various chemical structures that are more potent than the already existing drugs on the market. One of the first antibacterial agents used were inorganic mercury salts. However, the compounds had only a bacteriostatic activity. The agents bound to the sulfhydryl groups of bacterial enzymes and inhibited their growth. No longer in use is mercury chloride. Moreover, silver has good antibacterial activity and is used not only in the form of silver nitrate but also in the salts of sulfonamides, such as sulfadiazine and sulphathiazole for the treatment of burns. Other metal salts of zinc, copper and gold also show antibacterial avtivity [28]. Antibacterial therapy aims among others at interfering in the biosynthesis of bacterial cell wall or the synthesis of the bacterial DNA or proteins. Apart from zinc(II) pyrithione, which is used in the anti-dandruff schampoos, so far there are no copper(II), cobalt(II) or platinum(II) complexes used therapeutically. Nevertheless, there is much research going into finding a good agent that could be of better activity than known antibiotics. Most of all, much attention was paid to metal complexes of sulfonamides [29-33] and benzimidazoles [34-37].

8. BIOLOGICAL PROPERTIES OF COPPER

There has been much attention paid to copper because it is an essential element for life. It is associated with a number of copper-dependent enzymes that are key in biological processes. The most important copper-dependent enzymes in mammals [38,39]. Elevated copper levels in plasma can be important for the etiology of some illness [40].For example, copper ions are closely involved in neurodegenerative disorders [41-43], especially in Parkinson's disease [44-45]. Moreover, there has been interest in the medicaluses of copper, in particular as a complexing ion of known biologically active ligands and drugs. Throughout the years of scientific research copper(II) complexes have been found to possess various activities such as antiulcer [46], antiamoebic [47], antidiabetic [48] anticonvulsant [49], anti-inflammatory [50-52], antimicrobial [53] and antitumor [54]. In particular, anti-inflammatory, anti-microbial and anti-cancer activity of copper complexes has been studied. The three sub-chapters below briefly review copper complexes with such pharmaceutical properties. Another interesting compound is the copper(II) complex of 3,5diisopropylsalicylic acid, [Cu(II)(3,5-Dips)2]2 that shows not only anti-inflammatory but also antiulcer, anticarcinogenic, anticonvulsant, antidiabetic and analgesic properties [55-58].

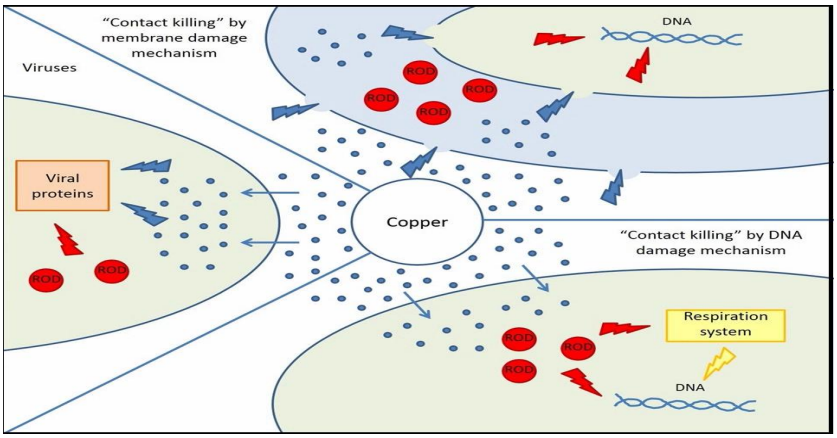

Fig. 4. Fiow diagram represent the biological properties of copper

9. BIOLOGICAL PROPERTIES OF COBALT

The word 'cobalt' is derived from the German 'kobalt', from kobold, meaning 'goblin', a word used by miners for the ore of cobalt [59]. Cobalt like copper is an essential trace element for higher organisms. It is required in the active center of coenzymes, the so called cobalamins (especially Vitamin B12 which regulates indirectly the synthesis of DNA). Moreover, there are at least eight cobalt-dependent proteins. Cobalamins alone are pharmaceutical agents and are treated in pathologies arising from a lack of vitamin B12 [60]. The cobalt complexes are of more limited medical usage compared to copper complexes. Since the first reported studies on the biological activity of cobalt complexes in 1952 [61],there has been interest in cobalt(III) complexes of bidentate mustards, which appear to act as hypoxia-selective agents [62]. Some complexes have already been found active not only against leukemia and lymphoma cell lines [63] but also against bacteria strains [64].Furthermore, cobalt complexes possess *in vivo* insulin-like properties [65], antifungal [66] and antioxidant activity [67].

10. BIOLOGICAL PROPERTIES OF ZINC

Zinc is an essential trace element. It is found thoughout the human body in a variety of tissues, such as skin, bone, liver, muscle or brain. In fact, this element is the most abundant transition metal in the brain after iron [68], and concentrations of zinc may reach 0.1-0.5 mM in the gray matter of the brain. It is also important for their biological activity as a constituent of proteins and enzymes that belong to cellular signaling pathways. Not only is it essential for the folding of DNA-binding domains of transcription factors (zinc-finger and hormone receptor families) [69] but zinc also has a variety of effects on the nervous system. It plays a crucial role in regulating the aspects of cellular metabolism, including protein, hormone, transcription and replication functions [70]. However, overabundant levels of zinc can lead to apoptosis and neuronal death [71]. It is to regulate the zinc balance in the body to maintain the homeostasis [72]. Both zinc overload and deficiency lead to pathologic processes in the central nervous system [73]. For example, zinc deficiency has been noticed in patients with head and neck cancer, It has also been associated with increased tumor size and the overall stage of the cancer [74]. A replenishment of zinc induced apoptosis in esophageal epithelial cells thus reducing the growth of the cancer [75]. Yet another way of action for zinc may be its effect on angiogenesis, which plays a critical role in carcinogenesis and tumour progression [76]. Elevated extracellular levels of zinc lead to the breakdown of the zinc transporting system of the plasma membrane. The resulting enhanced intracellular zinc concentration activates apoptosis [77]. However, an increased apoptosis *in vivo* may be a consequence of a decrease in zinc intracellular concentrations. Therefore, cellular zinc is also described as an inhibitor of apoptosis because its depletion causes death in cell lines [78].].A good antimicrobial and anti-inflammatory agent, zinc has also been successfully tested for healing zinc-deficient, chronic and surgical wounds by local administration [79].In the literature, there are many zinc complexes reported but only these associated with drugs in the treatment of Alzheimer's disease [80] or showing antimicrobial [81], anticonvulsant [82], anti-inflammatory [83], antidiabetic [84] or antitumor [85-87] activities are structurally described.

11. RESULT AND DISCUSSION

Metal resistance is simply the ability to maintain homeostasis of multiple metals at high external metal concentrations. Excretion of metal-sequestering compounds may contribute to resistance, e.g. of charged polysaccharides or carbonate, but since several frequently occurring transition metal cations are also essential, they have to be imported into the cell, which leads to toxic effects. Our goal is for you to understand why the chemical properties of these elements make them essential for life. We begin with a discussion of the strategies organisms use to extract transition metals from their environment. The section continues with a brief discussion of the use of transition metals in reactions that involve the transfer of electrons, reactions of small molecules such as O_2, Lewis-acid catalysis, and the generation of reactive organic radicals. There are three possible dietary levels for any essential element: deficient, optimal, and toxic, in order of increasing concentration in the diet. If the concentration of an essential element in the diet is too low, an organism must be able to extract the element from the environment and concentrate it. If the concentration of an essential element in the diet is too high, an organism must be able to limit its intake to avoid toxic effects. Moreover, organisms must be able to switch off the uptake process rapidly if dietary levels rise suddenly, and they must be able to store essential elements for future use.

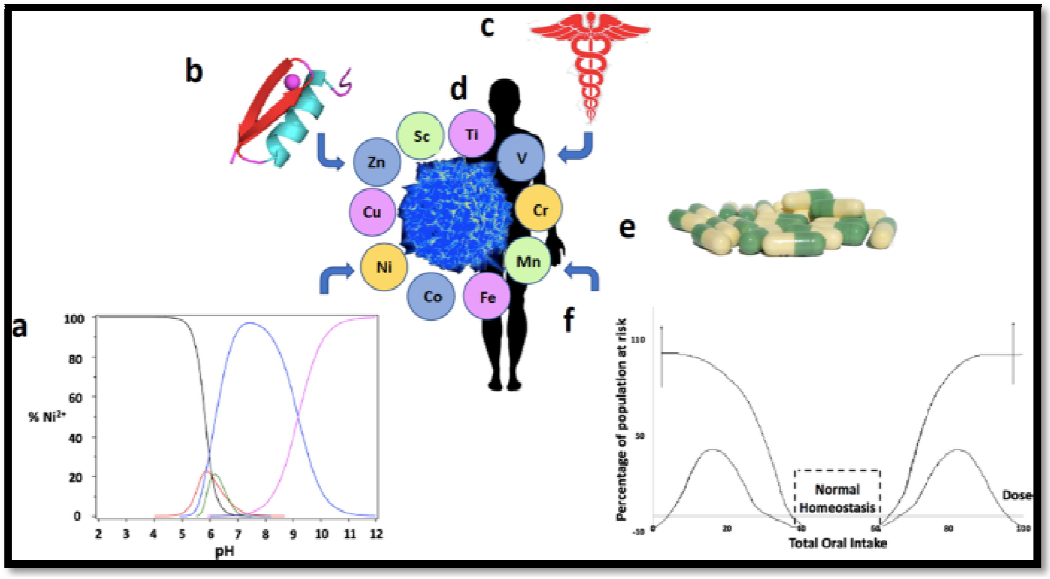

Fig. 5. Essential and trace element in our body system

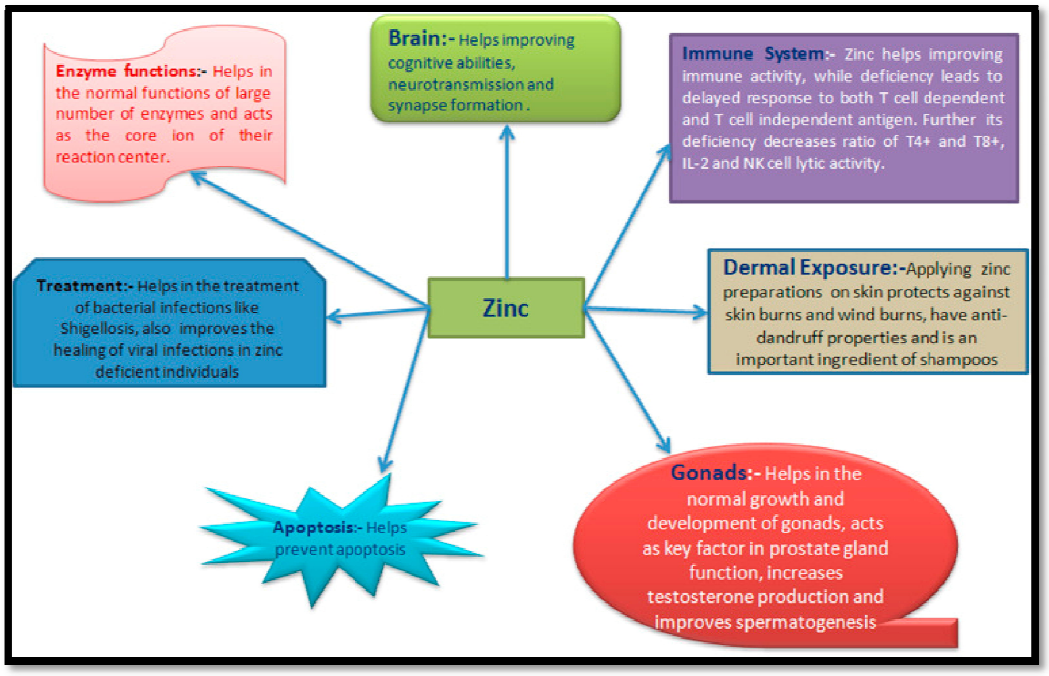

Fig. 6. Zinc containing biological activity in body system

Three separate steps are required for organisms to obtain essential transition metals from their environment: mobilization of the metal, transport of the metal into the cell, and transfer of the metal to where it is needed within a cell or an organism. The role of metal ions in biological systems has been realized for a long time. Some metals are essentials. Others are considered toxic. When it comes to transition metals, the story is not different from that of the main group metals. Some have no known biological effects, such as Scandium in its +2 and +3 oxidation states in its various isotopic forms. Some are hypoallergenic such as Titanium (Ti), while others are essential to all forms of life such as iron and zinc. It appeared that Zinc plays an

essential role in 300 enzymes in biota.The aim of this special issue is to make the biologically associated and related scientists pay more and close attention to the essential or the toxic effects of the elements in the first transition metal series of the periodic table. For example, iron (Fe2+/3+), by far, is the most important metal ion not only within the first transition series, but also within the entire periodic table. Without iron, there will be no life. The rest of the first transition metal series are: V, Mn, Co, Ni, and Cu. The experts on the biochemistry of these metal ions are welcome to contribute to this special issue. Biologists know the limited role of V in biology. Also, they know the role of Mn in photosynthesis, the role of Co in Vitamin B12, and the role of Ni in urease. We will give a very brief account for one of these remaining metal ions (copper). Copper exists in nature as Cu^{2+} which is the most stable oxidation state; this oxidation state is what always studied by researchers. Cu^{2+} is an essential trace metal ion involved in many metalloproteins including: ceruloplasmin, cytochrome oxidase, superoxide dismutase, dopamine-β-hydroxylase, ascorbate oxidase, lysyl oxidase, and tyrosinase. First-row transition metals play several roles in biological processes and in medicine, but can be toxic in high concentrations. Here the authors comment on the sensitive biochemistry and speciation chemistry of the first-row transition metals, and outline some of the remaining questions that have yet to be answered [88]. It Maintenance of human health and vitality requires the ingestion of trace levels of numerous inorganic elements, among them the transition metals iron (Fe), manganese (Mn), zinc (Zn), cobalt (Co), copper (Cu), nickel (Ni), molybdenum (Mo), vanadium (V), and chromium (Cr).

12. CONCLUSION

In general, transition metals are sequestered in organometallic complexes within our bodies, enabling their properties to be controlled and directed where needed, and their propensity to promote the generation of harmful reactive oxygen species is minimized. Transition metals are key components of numerous enzymes and electron transport proteins as well as the oxygen transport proteins hemoglobin and hemocyanin. Zinc finger motifs provide the DNA-binding domains for many transcription factors, while Fe-S clusters are found in many of the enzymes that participate in DNA replication and repair. Nutritionally or genetically induced deficiencies of these metals are associated with a variety of pathologic conditions including pernicious anemia (Fe), Menkes disease (Cu), and sulfite oxidase deficiency (Mo). When ingested in large quantities, most heavy metals, including several of the nutritionally essential transition metals, are highly toxic and nearly all are potentially carcinogenic [89].

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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