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Review Article

Medicinal Importance of Some Metal Cluster Compounds

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Abstract: Metal clusters are very interesting materials with highly active metal sites. Active metal sites are important for interaction with biological targets. In this review article we have summarized medicinal/biological importance of metal clusters compounds. We have presented the collection metal clusters having potential for the treatment of different fetal diseases like Cancer, Diabetic, Alzheimer, Cardiovascular disease, Hypertension, and Anemia etc. Thus the metal clusters are now getting prominence share in modern medicines.

Keywords: Metal Clusters, Cancer, Medicines, Metal Carbonyls, Organometallics

1. Introduction

Metals are present in our human body and perform many functions, e. g.; many metals such as copper (Cu) and zinc (Zn) are essential for a human health and protect us against many diseases. They are implicated as being involved in many degenerative diseases including atherosclerosis degenerative brain disorders, arthritis, cancers etc. Normally, the distributions and concentration of such metals are tightly controlled by human metabolic process and the causes of these metal imbalances which may be an important factor in all degenerative diseases. Chelation Therapy has shown promise in the treatment of many of these diseases; it is not desirable for a long term use as it also affects other essential biological functions. The metabolism of metal in biology is likely to treat the enormous potential to lead to healthier aging of our population. The experts in chelation therapy are in effort to develop effective chelation therapies in the median term and better understanding and treatment of degenerative diseases in long term. [1-4]

Metals being the important part of biological systems are of high interest in active form for the designing of new drugs. Among these metal compounds metal clusters are the materials having the most active metal atoms. Metal clusters are compounds that contain a group of two or more than two metal atoms having a direct and substantial metal-metal bond as shown in fig. 1. Generally cluster is group of bounded atoms or molecules that is between a molecule and a bulk solid in properties.

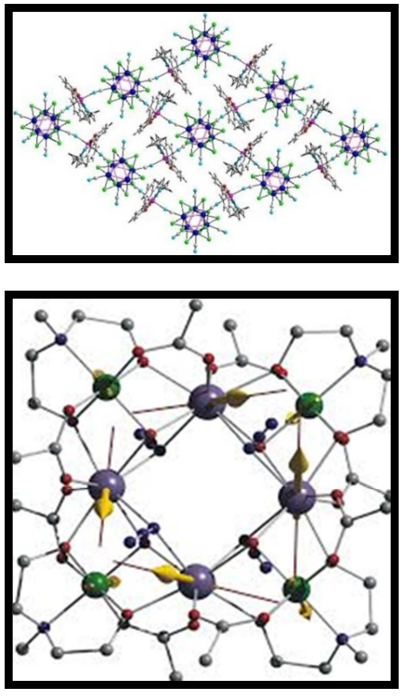


Figure 1. *Metal Clusters.*

The metal clusters may be homonuclear and heteronuclear. A homonuclear cluster has same kind of metal atoms whereas Heteronuclear clusters have different kinds of metal atoms. Metal clusters may be Atomic or Molecular. Mostly the transition metals and main group elements form cluster compounds. For transition metal cluster, the mostly used ligands are CO, alkenes and hydrides. [5-7]

Cluster study began to emerge in 1970-1980. Now much new advancement has occurred in this field about research point of view. These small particles have very unique properties and they can be used as new materialsin Nano chemistry, Analytical chemistry, in catalysis, As magnetic storage media, As electronic material. Now, metal clusters are getting important in medicinal chemistry.

There is not a great difference between the properties of a cluster and nano particles. The nanoparticles are now penetrating in medicinal chemistry so in this sense we can say that clusters can also be used as drugs. Application of metal cluster depends upon the nature of metal atoms, type of ligands, type of bonding, optical properties etc.

2. Some Metal Clusters and Their Functioning

There are two major types of clusters named homogenous and heterogeneous clusters. [8, 9]

2.1. Homonuclear Clusters

Homonuclear molecules, or homonuclear species, are molecules composed of only one type of element. Homonuclear molecules may consist of various numbers of atoms, depending on the element's properties. Some elements form molecules of more than one size. Noble gases rarely form bonds, so they only have one atom. The most familiar homonuclear molecules are diatomic, meaning they consist of two atoms, though not all diatomic molecules are homonuclear. Homonuclear diatomic molecules include hydrogen (H_2), oxygen (O_2), nitrogen (N_2) and all of the halogens. Ozone (O_3) is a common triatomic homonuclear molecule. Homonuclear tetratomic molecules include arsenic (As_4) and phosphorus (P_4).

2.1.1. Ruthenium Cluster

Cis platin, carbo platin and oxaloplatin can be used for proper treatment of cancer with minimum hazards Ruthenium metal clusters came in competition with Pt-complexes.

The development of metal based anticancer compound has traditionally focused on the development of ruthenium based anticancer compound which are operate via different mechanisms, as compared to use of Pt drugs. The structure of ruthenium cluster is given in figure 2. Indeed ruthenium complexes are less toxic toward the cancer cells in vitro and their property to bind DNA is lower. Two ruthenium compound Indazolium-trans (tetrachlorobis 1H-indazol) ruthenate (III)), termed KP1019 and Imidazoliumtrans-(tetrachloro (dimethylsulfoxi de) 1H-imidazole) ruthenate (III) termed NAMI-A in phase II clinically trials. The latter compound shows both antimetastatic and anti-angiogenic activity in preclinical method. Recently Ru compound organometallics rutherium (II) complexs, Ru (eta6-arene) cl2PTA) here arene, toiuene and p-cymene, PTA=1, 3, 5-triaza-7phosphadamaantane) also exibitsantimetastatic and anti angiogenic properties. While most of Ru cluster with low valency have CO, the biological importance of CO as essential mediator of numerous effects including anti-infalamatory and anti-proliferative activity. [10] Ruthenium cluster compounds are biologically active agents have been evaluated in 1950 by Dwyer and coworkers. They studied the effects of several Ru cluster compounds on mice and bacteria. A recent trend in medicinal chemistry is found that Ru drugs have high affinity for cancer targets with far less side effects. The final and most recent approach to ruthenium drugs design would be generation of further Ru- ODM cluster in which an organic molecule bind to the active site of an enzyme and the attached Ru ion binds to a nearby residue of the same protein. The energy interaction setup between the metal and the target that offers to the medicinal chemist a high energy mode of bonding which is not available in traditional medicines. Ru compounds have shown high anticancer activity in cells of human and animal. However its mode of action is unknown in most of cases. [11-19]

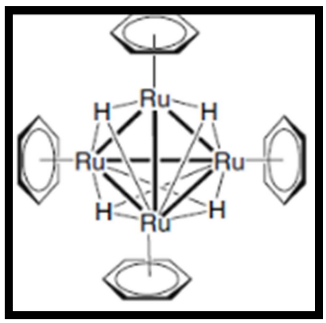
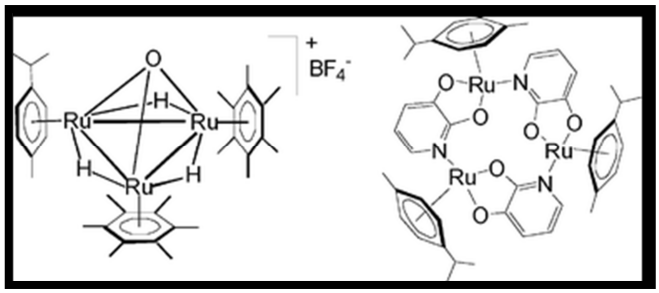


Figure 2. *Ruthenium metal cluster.*



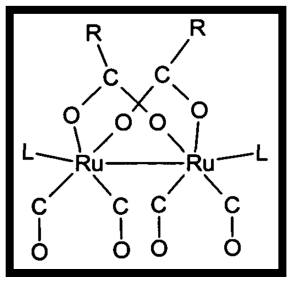


Figure 3. *Ruthenium clusters used in bio-imaging and bio-labeling.*

These clusters compounds also have potential for bioimaging and biolabelling. Ruthenium clusters used for such a purpose are given in figure 3. Several Ruthenium carbonyl complexes have been found to display cytotoxicity against breast cancer cell lines. For example, a Re (tricarbonyl) pentylcarbonato cluster compound is able to fight triple node negative human breast cancer cell. Rutheniumclusters show reproducible cytotoxic activity against A2780 human ovarian cancer cells in vitro. Sensitivity of these clusters was noted in breast cancer (figure 4) and non-small cell lung cancer cell lines (figure 5). [10, 20-22]

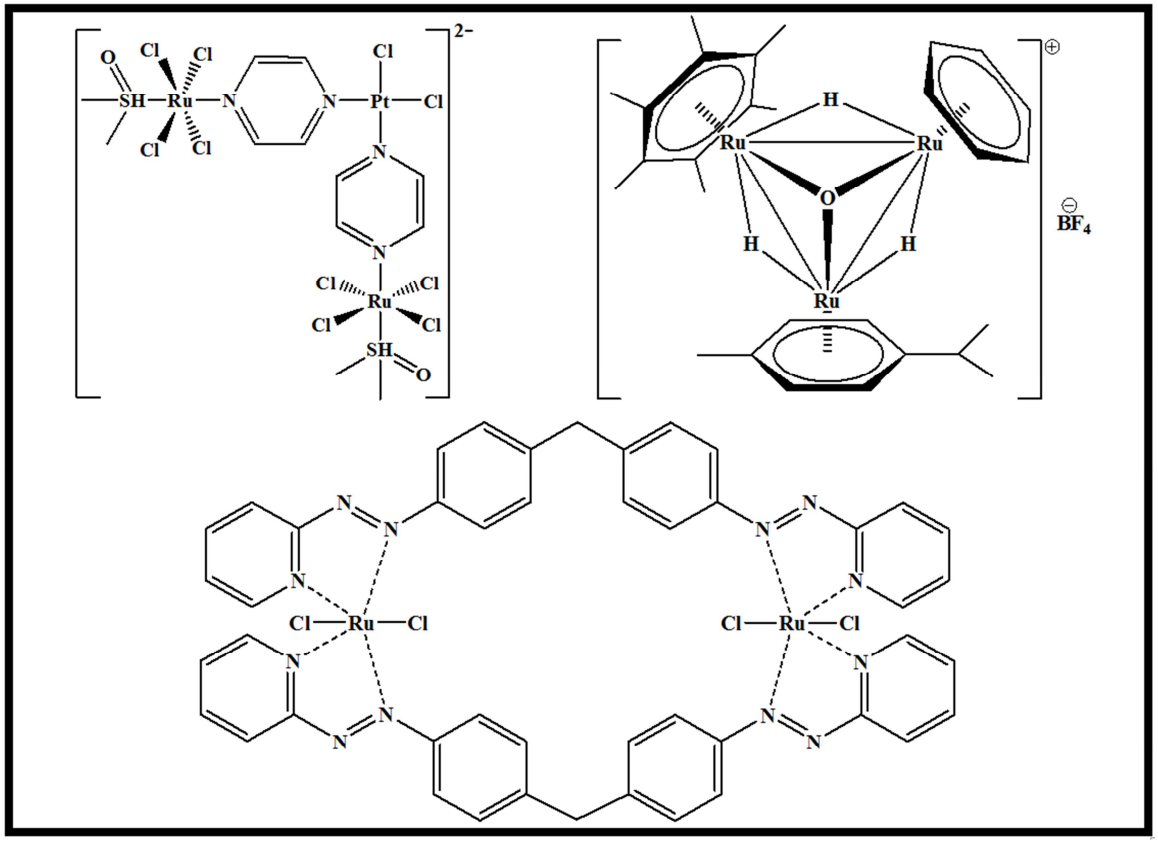


Figure 4. *Ruthenium clusters used in Human breast cancer treatment.*

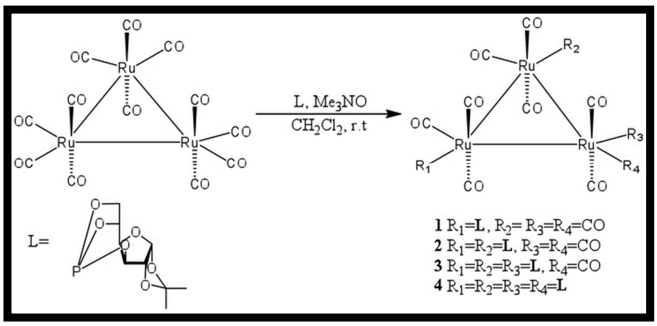


Figure 5. *Ruthenium clusters used in Human Lung cancer treatment.*

These Ru-clusters are under clinical trials. While using the Ru- clusters, permeability and retaining ability of cancer cells are increased in comparison to normal cells. Firstly large Ru-clusters can enter only through large perforation of cancer cells. Secondly cancer cells can retain them effectively. As the Ru-clusters link with DNA (figure 6) cause un-coiling of DNA by cross bonding. It leads to retardation or degradation of DNA as a consequence DNA can't make its copies and further cell division stop.

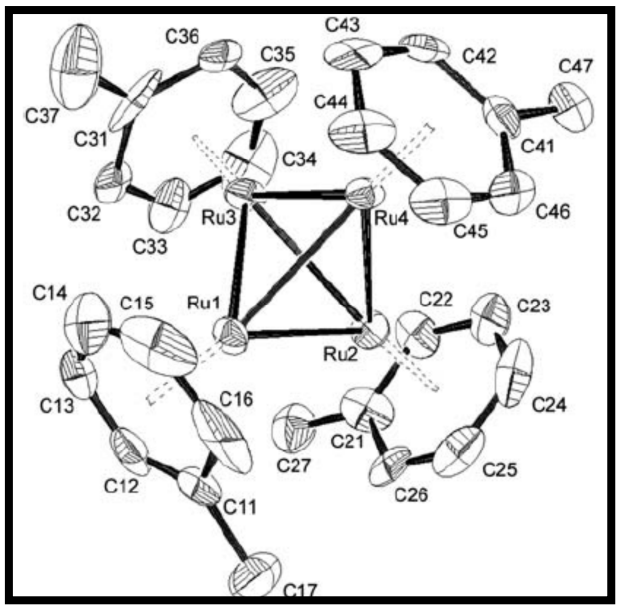


Figure 6. *Ruthenium cluster used in DNA degradation.*

Notable point in effectiveness and selective action of Ru-cluster is their miscibility in water. If they remain insoluble then how they can transported by the body fluids? These clusters are pH conscious due to which their solubility can be regulated by change in pH. For more proper selective action, drug can be bonded with macromolecules.

Ruthenium clusters such as Tetraruthenium clusters (Figure 7) are used for the treatment of Polio type virus 1. This virus is a major causes of physical disability in the entire world now a days. This cluster has mild toxicities in the healthy cells and has the ability to intercalate with the membrane of virus and damage it. [23, 24]

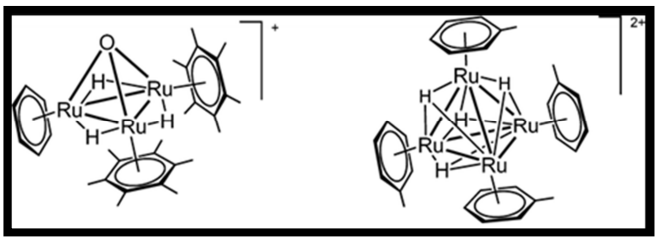


Figure 7. *Ruthenium clusters used in treatment of Polio type virus I.*

2.1.2. Vanadium Metal Clusters

Vanadium metal clusters are believed to have Biological and Medicinal uses. Vanadium Metal clusters have been shown to lower the growth of human prostate cancer cells and to reduce Bone Cancer and liver cancer in animals. Vanadium metal clusters can improve sensitivity to insulin in research has shown that vanadium metal clusters cause blocking of protein synthesis as well as oxidation of lipids which is considered a Primary step in development of "Cardiovascular diseases". Vanadium metal clusters are now the focus of many studies BIS (maltolatooxi-vanadium (BMON) (Figure 8) was the first vanadium cluster that increased effectiveness against diabetes.

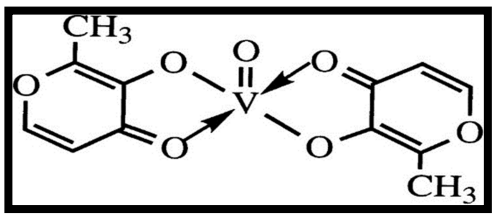


Figure 8. *Structure of Bis (maltolactooxivanadium) (BMON).*

Vanadium metal clusters use as potential therapeutic drugs in the treatment of diabetes by enhance the action of insulin. A new area in which vanadium metal cluters have demonstrated HIV-1 reverse transcriptase inhibition in vitro. [25]

2.1.3. Gold Clusters

Gold is a precious metal and is found in variety of forms has been used in medicine throughout the history of civilization; in 20th century gold complexes were found for the treatment of rheumatoid arthritis in 1985. The clinical use of gold is described focusing on the anticancer and antimicrobial properties of gold cluster compounds. Gold therapy is used as treatment for various inflammatory skin disorders such as pemphigus. Chrysotherapy treatment with gold drugs is now an accepted part of modern medicine. Gold cluster has been used to identify antitumor drug. Gold cluster compound exerts a number of effects on immune system. [26] Gold metal clusters also used as antigen carriers were shown to stimulate the phagocytic activity of macrophages and affect the functioning of lymphocytes, which is responsible for their immune-modulating effect. [27]

More recently many new and advanced techonologies are used which have ability to collect mainly or specially in the treatment of cancer. Gold nanostructures are very important in biomedical research due to their optical and chemical properties with biocompatibility. Photo thermal therapy is less dangerous than chemotherapy. In photo thermal therapy, light is absorbed and then converted into heat and this heat can cause the denaturation of protein and DNA of the targeted cell and cause non-repairable damage to the cancer cells.

Gold particles are passed through a cancerous cell or tumor with the help of a blood vessel which is directly attached to that respective cell or tumor. Gold nanocages have hollow interior and thin porous walls. Gold nanocages have size less than 50 nm and have strong resonance peak in NIR region at 810nm. Gold nanocages combined with cancer cell specific antibodies are very effective in photo thermal degradation of the cancer cells with much lower laser radiation (figure 9). Their small sizes also help these gold nanocages in better incorporation in the cancerous cells.

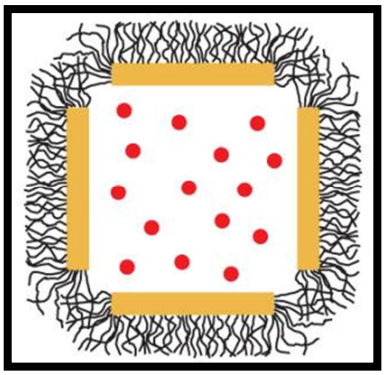


Figure 9. *Gold nanocage.*

Gold nanocages are cell specific and therefore cannot harm the healthy cells and very efficient clusters for photothermal therapy as shown on figure 10. [28]

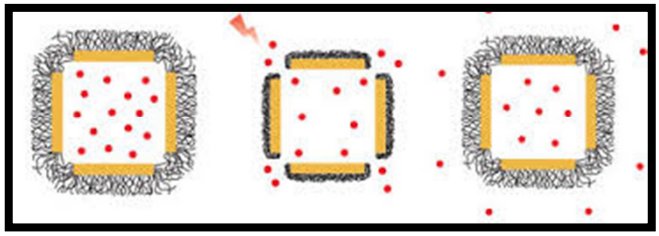


Figure 10. *Gold nanocages used in Photothermal therapy.*

The gold forms the complex with the cancer cells as shown in figure 10. The role of gold is just to prevent the oxidation. [26 - 30]

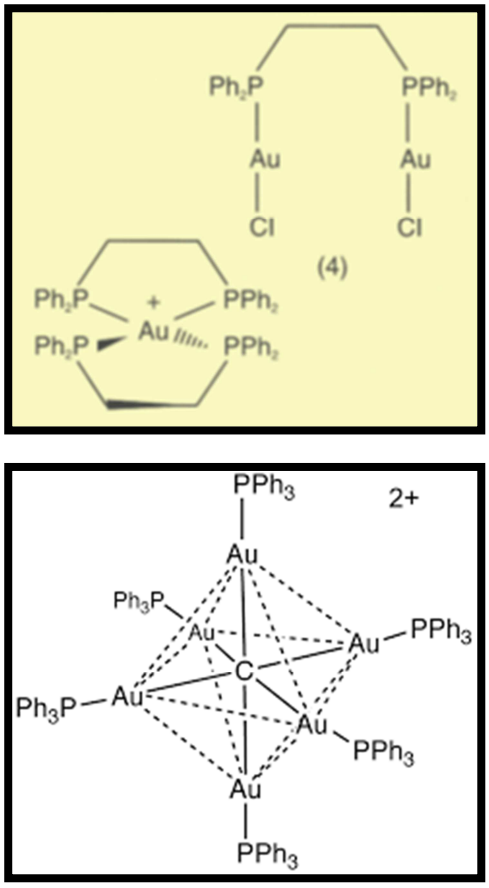


Figure 11. *Gold clusters used in Cancer cells.*

2.1.4. Silver Metal Clusters

Some Au and Ag clustersuse for simultaneous cancer cell targeting and imaging was demonstrated. Silver clusters are also used as antimicrobial agents for the treatment of various diseases such as cystic fibrosis and chronic lung cancers. For such a purpose the clusters used are Ag- N- Heterocyclic carbenes as shown in Figure 12 [20, 22, 31]

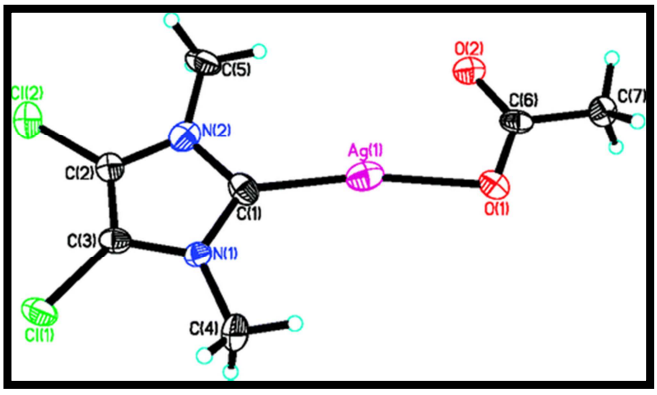


Figure 12. *Silver clusters used in Cyctic fibrosis and chronic Lung cancer treatment.*

2.1.5. Pt Metal Complexes [4, 32]

Pt metal clusters hydrolyses in vivo by loss of chlorides. The metal fragment apparently fits itself into the DNA chain structure, preferentially of tumor cells, and causes the tumor cells to die. Chemically stable luminescent Pt clusters have recently been reported as suitable for live-cell imaging with two-photon excitation and TRLM. Pt clusters also has anti cancer activities. Platinum is well known for its anticancer activity used as cisdiaminedichloroplatinum (*(II)* (CDDP). [16, 33-36] The main mechanism of action of CDDP involves covalent bonding with DNA, leading to the formation of adduct and cross links and at least to apoptosis as shown in the figure 13. Cisplatin, it was a massive success to launch the medicinal inorganic chemistry. Now many compare able anticancer agents are being synthesized but two are more important Carboplatin and Oxaplatin. [4]

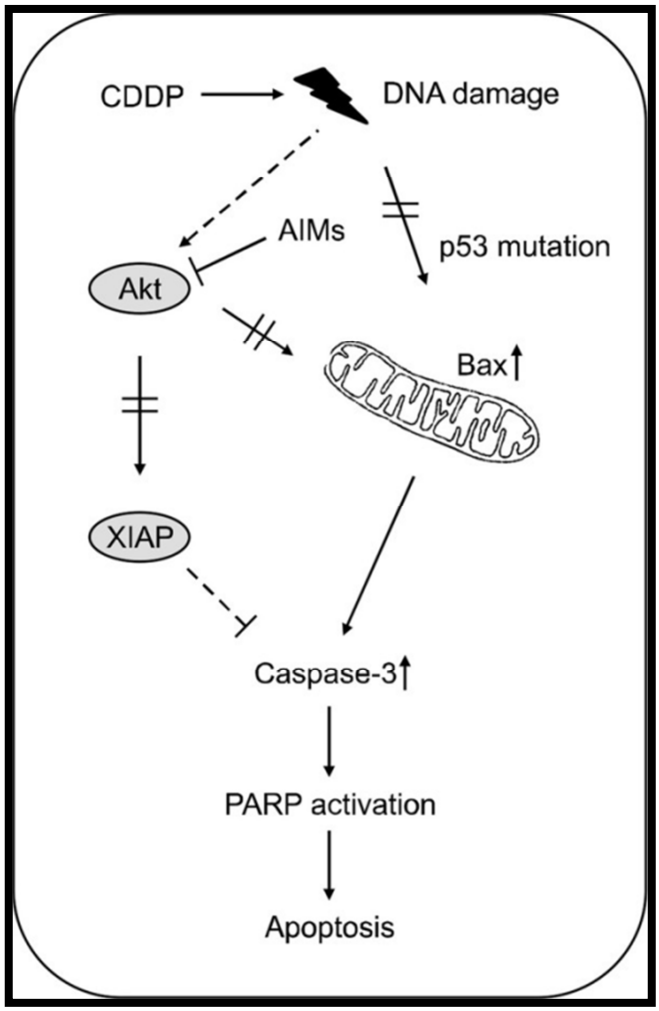


Figure 13. *Role of platinium cluster in Apoptosis.*

2.1.6. Osmium Metal-Clusters

Osmium-arene clusters have cytotoxic activity against human A549 and A2780 ovarian cancer cells. Another clinical use of osmium clusters appears to be for synovectomy in arthritic patients in Scandinavia. The lack of reports of long-term side effects suggest that osmium clusters itself can be biocompatible, although this depends on the osmium compound administered. [20, 22]

2.1.7. Cobalt Cluster [37, 38]

The cobalt cluster show higher anticancer activity than CIS PLATIN. [37, 38] The structure of cobalt cluster used for

anticancer purpose is given in figure 14.

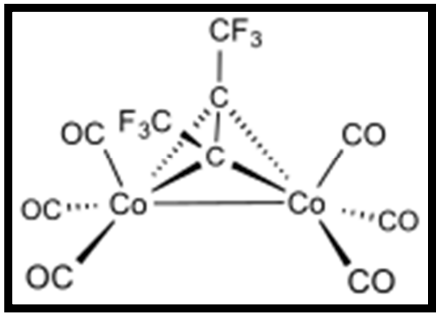


Figure 14. *Cobalt cluster having anti cancer activity.*

2.1.8. Molybdenum Metal-Clusters

Mo metal clusters have been used in the treatment of various conditions including anemia and as a general tonic for restoring appetite after convalescence. Mo metal clusters can be used for prevention of dental caries. Effect of molybdenum clusters on the immunological reactivity of organisms was also noted. The addition of molybdenum clusters to the diet of rabbits daily for up to 12 months increased the immunological reaction towards Bact. proteus OX19 culture. A study of molybdenum (VI) clusters as potential anti-diabetic agents is reported. These clusters show anti-diabetic properties by enhancing insulin signaling. The most important role of the molybdenum metal clusters in living organisms is as a metal cluster of heteroatom at the active site in certain enzymes. [20, 22]

2.1.9. Poly Nuclear Metal-Clusters

Their strong isomorphism and anomalous scattering signal of poly nuclear metal clusters is particularly useful for phasing structures of large macromolecules and complexes, especially at low resolution as shown in figure 15. The most popular structure for phrasing. [20, 22]

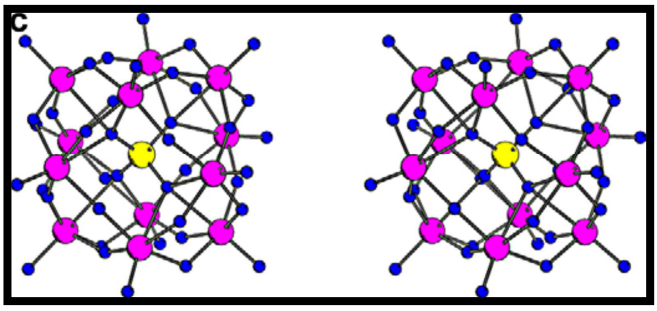


Figure 15. *Structure of Polynuclear cluster.*

(i) CO releasing metal cluster compounds as drugs [39-41]

Carbon monoxide releasing metal cluster compounds are used as vasodilators. Vasodilatation refers to the widening of blood vessels. Drugs that cause vasodilatation are termed as vasodilators. Introduction of suitable co-ligands in metal carbonyl clusters has provided us with the opportunity to finely tune carbon monoxide releasing clusters for therapeutic purposes. carbon monoxide is naturally produced in living system and causes vasodilatation apart from anti-inflammatory and antiapoptotic characteristics. Several metal clusters having manganese, cobalt, nickel and ruthenium have been investigated for delivering carbon monoxide in living systems. Especially $Mn_2(CO)_{10}$ release carbon monoxide under physiological conditions causing long-lasting vasodilatation and it does not pose any detectable toxicity to cells. Carbon monoxide releasing clusters also have cardio protective properties due to widening of heart vessels by carbon monoxide. Carbon monoxide releasing molecular metal clusters are also being used as potential hypertensive and anti-inflammatory drugs including allergic inflammation and protectors against vascular injury. They also minimize the chances of transplant related vascular arteriosclerosis. CO is also known to protect from organ graft rejection, oxidative tissue damage, septic shock and involved in blood pressure regulation. so there are numerous potential applications of carbon monoxide releasing molecules in the clinic as shown in figure 16.

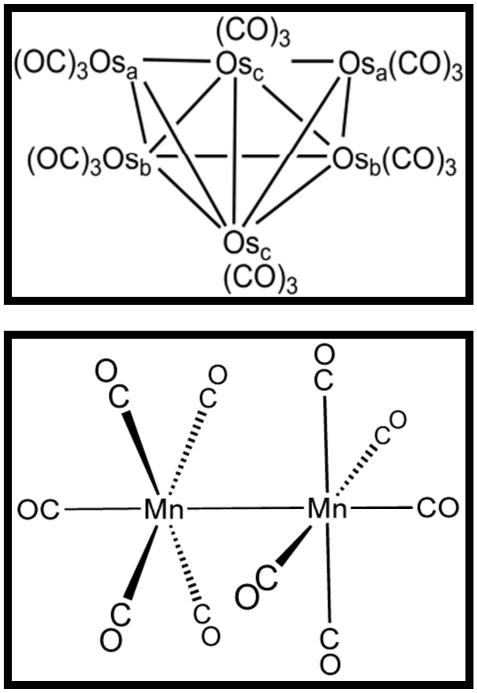


Figure 16. *Structures of carbonyl releasing metal cluster compounds.*

(ii) Rhenium compound [13]

A dirhenium complex cis [Re2 (GABA) 2Cl5(H2O)] Cl.2H2O having the zwitter ionic g-amino butyrate ligands. It is prepared by spectral method and crystallography. The complex structure is binuclear complex (cataion). (Re-Re) having cis oriented double carboxylate as bridge and two Rhenium centre four equatorial chloride and aqua which are weekly bonded the chloride at the axial position

The pedal wheel carboxylate complex of rhenium it can bind the DNA and inhabit the replication and protein synthesis same to cisplatin dirhenium (lll) aliphatic carboxylate when it introduced in the liposome in tumour bearing animal it inhabit tumor growth by 20-30% At this time these species reveal biochemical and potential modulators of cisplatin action It decrease the toxicity and enhance efficiency. Both dirhenium and cisplatin causes to interpretation in the tumor growth and

disappearance of cancer cell in the experimental animal. The structure of rhenium cluster used for such purpose is given in figure 17. The dirhenium carboxylate also stabilize the red blood cell against the haemolysis as provided by in vivo and vitro studied. The zwitterionic g-aminobutyrate (GABA) causes the preparation of cation species [Re2 (GABA) $2Cl4]^{2+}$.

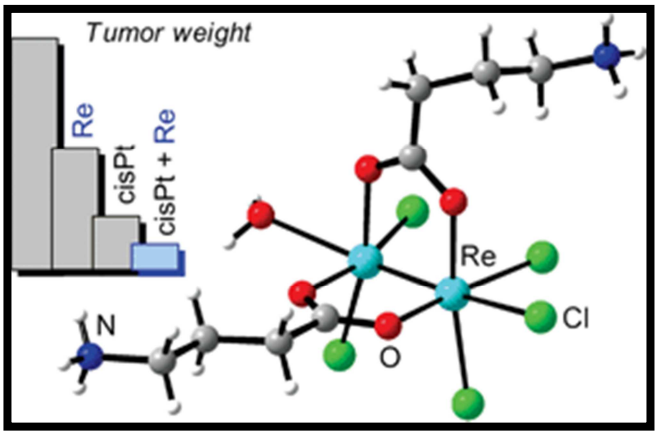


Figure 17. *Rhenium cluster used in treatment of tumor.*

The rhenium and cisplatin both together introduced in cells. The Significant effect is observed these also control the growth of the tumour.

The growth of the tumor rapid in 21 days and the size of tumor reached to 1/3 to total weight of animal the cisplatin decrease the tumor growth. During this the weight of tumor was less but the mortality level remain same 20-30. The dirhenium (lll) dicarboxylate complex have special antitumor activity. It have higher activity then the other alkyl carboxylate which previous investigated. This cause the more application for antitumor action. These complexes were studied for the tumor growth about 60% and also stabilize the red blood cells. [42]

2.2. Heterogenous Clusters

2.2.1. Fe-Ni Clusters

Iron–nickel i. e. Fe–Ni structures displaying polyhedral frameworks held together by two or more metal–metal bonds per linkage, where the metal atoms are located at the peaks of closed, triangulated polyhedral.

2.2.2. Fe-Ni Clusters in Biology

Fe-Ni metal clusters are vital for energy production in many bacteria. A primary source of energy in bacteria is oxidation and reduction of H_2 which is performed by hydrogenase enzymes. The hydrogenase enzymes are arranged about as Fe-Fe or Fe-Ni active site. The active site Fe-Ni containing hydrogense enzyme is composed of one or more bridging sulfur, carbonyl, cyanide and terminal sulfur ligands as shown in figure 18. The non-bridging sulfur ligands cysteine amino acids residue that attached to the active site. Oxidation state of Fe-Ni core have been observed in enzymes. Active site of Fe-Ni active site in (A) inactive oxidized and (B) the active reduced form. [8, 9]

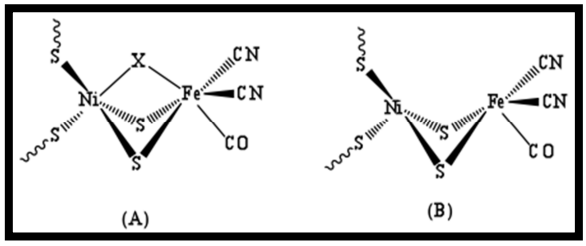


Figure 18. *Structures of Fe-S heterogenous clusters.*

2.2.3. Fe- S Clusters in Biology [43]

Iron sulphur (FeS) clusters containing proteins are very important in various very necessary processes like the photosynthesis in plants, respiration in both plants and animals, and for the nitrogen fixation bacteria in order to maintain the amount of nitrogen in the atmosphere. Their composition may be vary as well as their ability To accept or donate single electron or Fe. They catalyze various enzymatic reactions as well as some time act as regulatory properties.

MITONEET (MNT) is an outer sphere membrane of the mitochondria. And is the target of the thiazolidinemedione a diabetic drug. This drug has a unique fold and also has a cluster [2Fe-2S]. This cluster is labile in this drug. The liability of this cluster is due to the 1-histidine and 3-cys-coordination of MNT and this liability is strongly dependent upon the single histadine ligand. MNT is similar to [2Fe-2S] shuttle protein in most of its properties.

[2Fe-2S] cluster is transferred in between MNT which is oxidized and apo-ferrodoxine (a-fd). This transformation is second order and unidirectional. And it's comparable to that of Fe-S transfer protein. A very well known diabetic drug which is commonly named as pioglitazone stops the transfer of iron from MNT to mitochondrial membrane. So we can say that pioglitazone effect the property of [2Fe-2S] cluster transfer in the environment of the cell.

This discovery is very important in light of role of Fe overload in diabetes Miletus. This finding suggests that MNT in [2Fe-2S] and Fe transfer towards the acceptor protein and this idea that "the pioglitazone's anto diabetic action may be regarded as due to its inhibition of transfer of MNT'S cluster [2Fe-2S].

As we know that in the mammals cells mitochondria are the key source of energy so if their function uis disturbed by such accommodation of metal are mismanagement of such clusters thaycause metabolic disorder like type II diabetes.

3. Conclusion

The fight with cancer is seems to be won by the use of metal compounds as many of the metal clusters are getting more and more interest. The metal clusters are providing methods for treatment of cancer other than chemotherapy. As they are now merging in medical imaging as well.

Metal clusters of Re, Au, Ag, Co and Mo are more important in this regard and going to be the future drugs. Au compounds are of special interest in photo-thermal therapy and Mo, Mn carbonyls are very special to control carbon

monoxide release regulation.

In addition to cancer, metal clusters are useful in the treatment of other diseases like diabetes, Alzheimer, cardiovascular disease, hypertension, anaemia and others. The metal clusters are found active to repair the infections due to microbes.

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