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# Chemical and Biological Properties of vanadium and Iron compounds in relation to cancer treatment and other Biological Applications- A review

**Ab. Rashid Wani[1]*, Ghulam Mohammad Jan[2]**
*1.Department of Chemistry, Govt. Degree College Boys Dooru Anantnag J&k (India)*
*2.Department of Chemistry, Govt. Degree College Boys Anantnag J&k (India)*

## ABSTRACT

Overall, we are convinced that in the future the field of medicinal inorganic chemistry will be a key part of drug development for personalized medicine, allowing also considerable advances in predictive medicine. However, we should also fight against the prejudice associated to metal-based drugs, mostly in terms of in vivo toxicity. Thus, as bioinorganic chemists, we should be able to address the difference between the toxicity related to the "naked", non-coordinated metal ion, and that of the corresponding metal stabilized by the coordinating ligand(s). Moreover, the toxicity of metal complexes is a multifaceted subject during the development of metal-based drugs as it primarily depends on the type of selected application. In the case of metal-based radiopharmaceuticals for diagnosis or therapy toxicity is not the main matter of concern due to the low concentrations of metal-complexes administered to the patients. In order to exert pharmacological effects (e.g. cisplatin is activated by hydrolysis inside cancer cells), however, further studies are necessary to "fine tune" the stability metal complexes while maintaining their biological activity and reduce their side-effects.

**Keywords:** Coordinated metal complex, Cisplatin, Toxicity, Cancer cells.

*Corresponding Author Email: abwani001@gmail.com
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# INTRODUCTION

Vanadium is a group 5d transition metal possessing certain chemical and biochemical properties. A variety of vanadium compounds have been synthesized so far , in an effort to offer better tolerance, more potent action, a better selectivity and less toxicity in cancer treatment. Chemical and biochemical characteristic determine the anticancer effects of vanadium compounds. A relationship has been found between the chemical composition and the antitumour activity and toxicity of peroxovanadates, this was shown to depend upon the type of the heteroligand[1]. At non-toxic concentration the identity of the ancillary ligand of the peroxovanadium complex may play a significant role on the cell cycle arrest exerted by these complexes on tumour cell lines[2]. Concomitant treatment with vanadate(IV) and peroxide($H_2O_2$) enhances the biological effects of the metal in various cell lines, due probably to the formation of peroxovanadate. Following chart is a schematic presentation of the action, through which the antitumor effects of vanadium are exerted (PTPs, Protein Tyrosine Phospahatases, PTKs, Protein Tyrosine Kinases).

**Antidiabetic use of Vanadium**

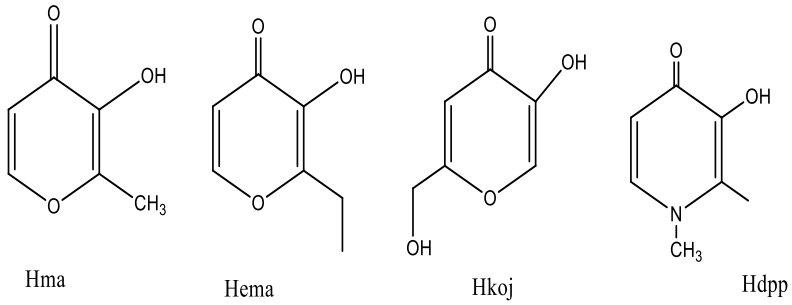
Many compounds have been proposed as 'insulin mimics.' This term may be somewhat misleading in that vanadium can never entirely replicate insulin's plethora of effects[72]. Vanadium can mimic some, but not all, of insulin's actions and, most notably, does not function in this capacity in the complete absence of endogenous insulin. Thus, some investigators prefer to think in terms of 'insulin' enhancement' for characterization of vanadium's anti-diabetic effects[3].Here in we use these terms somewhat interchangeably, with this proviso in mind.

**V(IV) Insulin enhancing agents**

**Pyronates and Pyridinonates**

As ligands for the design of vanadium complexes appropriate for use as insulin enhancing agents, 3-hydroxy-4-pyrones have proven to be exemplary. Maltol (Hma) and derivatives tend to possess moderate intrinsic bioactivity and a low toxicity profile[4], thus, they are very good spectator ligands in biological applications[75.]. Both maltol and ethyl maltol are by themselves approved food additives in many countries. In addition, Hma is well known for formation of stable, neutrally charged metal complexes which have an optimum combination of water- solubility, reasonable hydrolytic stability, and significant lipophilicity [5-8]. Pyrones and pyridinones can act as anionic chelating, bidentate O,O' ligands towards a number of biologically active metals[9-13].

Ligands structurally related to maltol include kojic acid (Hkoj), and Hdpp (1,2-dimethyl-3-hydroxy-4-pyridinone), both of which have substituents that can alter selectively the water-solubility, hydrolytic stability and lipophilicity of their metal complexes[14]. (Scheme 1)

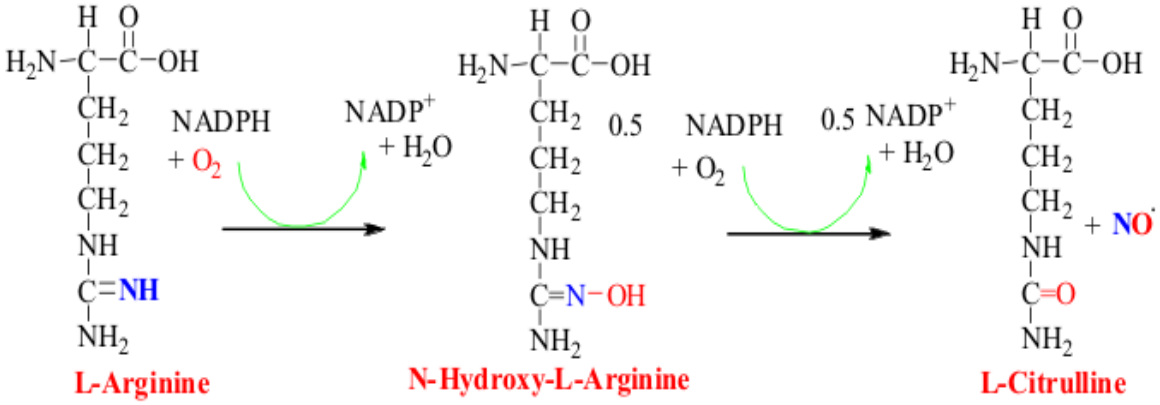



**Scheme 1 Insulin enhancing agents**

Bis(maltolato) oxovanadium (IV), BMOV or $VO(ma)_2$ (1), consists of vanadyl [$VO^{2+}$] bound to the anion of maltol (3-hydroxy-2-methyl-4-pyrone, Hma) Interest in maltol and close analogues , such as ethylmaltol (3-hydroxy-2-methyl-4-pyrone, Hma) and kojic acid (5- hydroxy-2-hydroxymethyl-4-pyrone,Hkoj), is partly due to their ability to deprotonate readily (pKa values for Hma =8.38, Hema =8.78, Hkoj = 7.72) .

**Trasition metal nitrosyls**

In 1980s nitric oxide (NO.), synthesized endogenously by the enzyme NOsynthase (NOS), shown below, was discovered to be one of the most important physiological regulator, including cardiovascular control (blood pressure regulation), neuronal signaling, platelet activation, immune[18] response, and as agents for defense mechanisms against microorganisms and tumors. (Scheme 2)




**Scheme . *The reaction catalyzed by nitric oxide synthase (NOS)***

The enzyme NOS converts L-arginine (an amino acid available in living organism) to citrulline and NO. The Co-substrates for the reaction include NADPH and O2.

The recent surge of investigations to[15] the chemistry of transition metal nitrosyls by inorganic biochemists and biologists is largely due to the Nobel Prizwinning discovery that endothelium-derived relaxing factor is the nitric oxide and to the realization that nitric oxide is implicated in a multitude of physiological and pathophysiological functions. Nitric oxide has been shown to have many bioregulatory functions in mammalian including cardiovascular control, neuronal signaling and an agent for defense mechanism against microorganism and tumours. As a result of these diverse and important applications many books, reviews and special topic papers are devoted to transition metal nitrosyl chemistry.

The nitrosyl group's ability to bind to transition metals in a linear or a bent fashion , to behave as $NO^+$ or $NO^-$ and to influence, as well as be influenced by, other ligands in the coordination environment has been of interest to coordination chemists and theoretical chemists for decades . Catalytic applications of transition metal nitrosyl complexes and $[Mo(NO)_2(acac)_2]$ (acacH = acetylacetone) as precursors8–12 have been carried out in our laboratory.

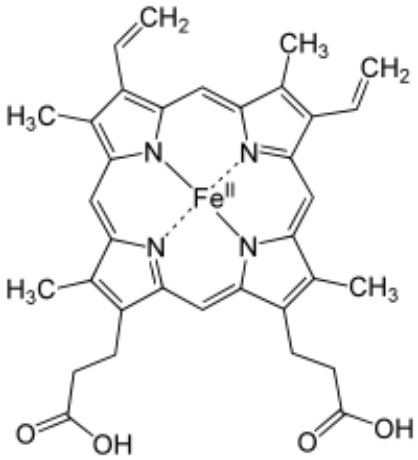
In excessive synthesis of NO, the increased level of NO can overwhelm cardiovascular control, leading to acute drop in blood pressure and renal (relating to kidneys) failure. This hypotension does not always respond well to conventional therapy such as intravenously administered adrenaline and dopamine. An alternative remedy may however be, to remove NO by use of a high affinity, non-toxic scavenger.

The ability of transition metal complexes, particularly of ruthenium, iron, manganese, molybdenum and cobalt (mostly of $d^5$ and $d^6$ systems), to both scavenge and release nitric oxide has generated a new interest in nitrosyl complexes as metallopharmaceuticals.

**Human Iron Metabolism**

Human iron metabolism is the set of chemical reactions maintaining human homeostasis of iron. The control of this necessary but potentially toxic substance is an important part of many aspects of human health and disease. Hematologists have been especially interested in the system of iron metabolism because iron is essential for red blood cells, where most of the human body's iron is contained. Understanding this system is also important for understanding diseases of iron overload, like hemochromatosis, and iron deficiency, like iron deficiency anemia[50].

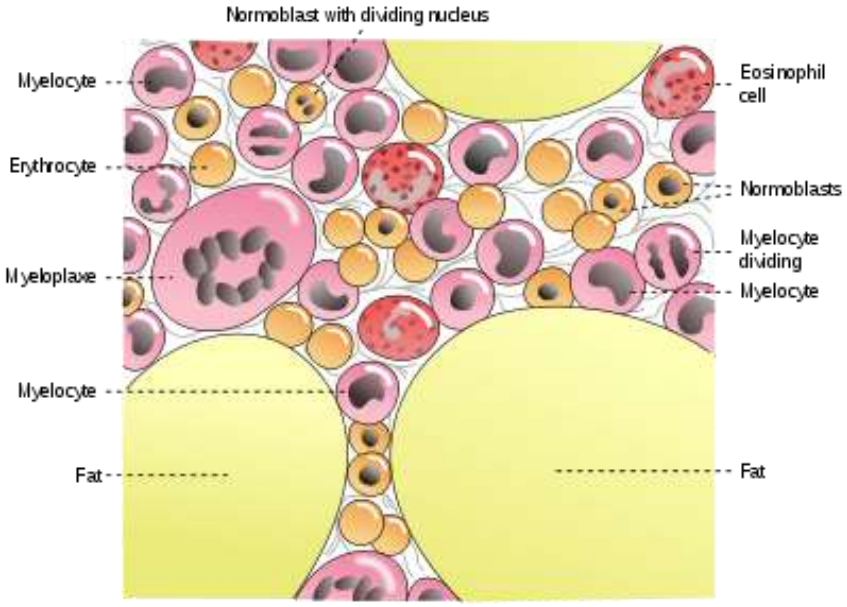
**Importance of iron regulation**




**Scheme 3: Heme b; "Fe" is the chemical symbol of iron, II indicates its oxidation state.**

Iron is an absolute requirement for most forms of life, including humans and most bacterial species, because plants and animals all use iron; hence, iron can be found in a wide variety of food sources.

Iron is essential to life due to its unusual flexibility to serve as both an electron donor and acceptor. Iron can also be potentially toxic. Its ability to donate and accept electrons means that if iron is free within the cell, it can catalyze the conversion of hydrogen peroxide into free radicals. Free radicals can cause damage to a wide variety of cellular structures, and ultimately kill the cell. To prevent that kind of damage, all life forms that use iron bind the iron atoms to proteins. That allows the cells to use the benefits of iron, but also limit its ability to do harm [16-17] .The most important group of iron-binding proteins contains the heme molecules, all of which contain iron at their centers. Humans and most bacteria use variants of to carry out redox reactions and electron transport processes. These reactions and processes are required for oxidative phosphorylation. That process is the principal source of energy for human cells; without it, most types of cells would die.




**Scheme 4: Body Showing how iron is Stored in the body**

**Absorbing Iron from the Diet**

The absorption of dietary iron is a variable and dynamic process. The amount of iron absorbed compared to the amount ingested is typically low, but may range from 5% to as much as 35% depending on circumstances and type of iron. The efficiency with which iron is absorbed varies depending on the source. Generally the best-absorbed forms of iron come from animal products. Absorption of dietary iron in iron salt form (as in most supplements) varies somewhat according to the body's need for iron, and is usually between 10% and 20% of iron intake. Absorption of iron from animal products, and some plant products, is in the form of heme iron, and is more efficient, allowing absorption of from 15% to 35% of intake. Heme iron in animals is from blood and heme containing proteins in meat and mitochondria, whereas in plants, heme iron is present in mitochondria in all cells that use oxygen for respiration.

Like most mineral nutrients, the majority of the iron absorbed from digested food or supplements is absorbed in the duodenum by enterocytes of the duodenal lining. These cells have special molecules that allow them to move iron into the body. To be absorbed, dietary iron can be absorbed as part of a protein such as heme protein or must be in its ferrous $Fe^{2+}$ form. A ferric reductase enzyme on the enterocytes' brush border, Dcytb, reduces ferric $Fe^{3+}$ to $Fe^{2+}$ [18] .A protein called divalent metal transporter 1 DMT1, which transports all kinds of divalent metals into the body, then transports the iron across the enterocyte's cell membrane and into the cell.

These intestinal lining cells can then either store the iron as ferritin, which is accomplished by $Fe^{3+}$ binding to apoferritin(in which case the iron will leave the body when the cell dies and is sloughed

off into feces) or the cell can move it into the body, using a protein called ferroportin. The body regulates iron levels by regulating each of these steps. For instance, cells produce more Dcytb, DMT1 and ferroportin in response to iron deficiency anemia [19]

The human body's rate of iron absorption appears to respond to a variety of interdependent factors, including total iron stores, the extent to which the bone marrow is producing new red blood cells, the concentration of hemoglobin in the blood, and the oxygen content of the blood. The body also absorbs less iron during times of inflammation. Recent discoveries demonstrate that hepcidin regulation of ferroportin is responsible for the syndrome of anemia of chronic disease.

While Dcytb is unique to iron transport across the duodenum, ferroportin is distributed throughout the body on all cells which store iron. Thus, regulation of ferroportin is the body's main way of regulating the amount of iron in circulation.

Hephaestin, a ferroxidase that which can oxidize $Fe^{2+}$ to $Fe^{3+}$ and is found mainly in the small intestine, helps ferroportin transfer iron across the basolateral end of the intestine cells.

**Reasons for Iron Deficiency**

Iron is an important topic in prenatal care because women can sometimes become iron-deficient from the increased iron demands of pregnancy.

Functional or actual iron deficiency can result from a variety of causes, explained in more detail in the article dedicated to this topic. These causes can be grouped into several categories:

- Increased demand for iron, which the diet cannot accommodate.
- Increased loss of iron (usually through loss of blood).
- Nutritional deficiency. This can result due to a lack of dietary iron or consumption of foods that inhibit iron absorption, including calcium, phytates and tannins. Black tea steeped for long has high tannins.
- Inability to absorb iron because of damage to the intestinal lining. Examples of causes of this kind of damage include surgery involving the duodenum, or diseases like Crohn's or celiac sprue which severely reduce the surface area available for absorption.
- Inflammation leading to hepcidin-induced restriction on iron release from enterocytes.

**How cells get their iron from the body**

As discussed above, 60% or more of the iron in the body is located in hemoglobin molecules of red blood cells, and much of the rest is in ferritin storage form in the liver and other places, the amount of this varying widely between persons. When red blood cells reach a certain age, they are degraded and engulfed by specialized scavenging macrophages. These cells internalize the iron-containing hemoglobin, degrade it, put the iron onto transferrin molecules, and then export the

transferrin-iron complexes back out into the blood. Most of the iron used for blood cell production comes from this cycle of hemoglobin recycling.

All cells use some iron, and must get it from the circulating blood. Since iron is tightly bound to transferrin, cells throughout the body have receptors for transferrin-iron complexes on their surfaces. These receptors engulf and internalize both the protein and the iron attached to it through receptor-mediated endocytosis. Once inside, the cell transfers the iron to ferritin, the internal iron storage molecule which is present in all cells. In iron deficiency, transferrin receptor production will increase. [20]

**Biomineralisation**

Biomineralisation processes are essential for human health in the formation of bones and teeth and in the storage of iron in ferritin. Malfunctions of these processes are responsible for serious birth deformities and other diseases. Hence, the genetic control of such processes needs to be better understood. In addition biomineralisation processes have essential roles in the lifecycle of serious diseases such as malaria, where the parasite causes the biomineralisation of heme groups that would otherwise be toxic to the invading parasite. There is growing evidence that most anti-malarials target this biomineralisation, hence a better understanding of the process will lead to better treatments for malaria

## CONCLUSION

Probing those low-capacity enzyme systems in vivo is a challenging task, being much dependent not only on the target selective uptake, but also on the high affinity of the radioprobe to the enzyme. Thus, the use of highly potent inhibitors and/or substrates of enzymes is always mandatory for probing enzyme levels in vivo. Overall, we are convinced that in the future the field of medicinal inorganic chemistry will be a key part of drug development for personalized medicine, allowing also considerable advances in predictive medicine. However, we should also fight against the prejudice associated to metal-based drugs, mostly in terms of in vivo toxicity. Thus, as bioinorganic chemists, we should be able to address the difference between the toxicity related to the “naked”, non-coordinated metal ion, and that of the corresponding metal stabilized by the coordinating ligand(s). Moreover, the toxicity of metal complexes is a multifaceted subject during the development of metal-based drugs as it primarily depends on The type of selected application. In the case of metal-based radiopharmaceuticals for diagnosis or therapy toxicity is not the main matter of concern due to the low concentrations of metal-complexes administered to the patients.

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