CompSci Journal
Double Blind Peer Reviewed, Open Access International Research Journal.
ISSN: 3067-3089 | Website: https://csjour.com | Volume-2, Issue-2 | April - 2026

Original Article

Biological Importance of Transition Metals

More A. L.[1], Chougule A. M[2]., Kadam S. S.[3]
[1]Department of Chemistry, BV'S Matoshri Bayabai Shripatrao Kadam Mahavidyalaya, Kadegaon, Dist- Sangli, (MS), India
[2]Department of Industrial Chemistry, Dayanand Science College, Latur, (MS), India.
[3]Department of Physics, BV'S Matoshri Bayabai Shripatrao Kadam Mahavidyalaya, Kadegaon, Dist- Sangli, (MS), India

Manuscript ID:
CSJ-2026-020212

Volume 2

Issue 2

Pp. 55-61

April 2026

ISSN: 3067-3089

Submitted: 08 Mar. 2026

Revised: 16 Mar. 2026

Accepted: 06 Apr. 2026

Published: 30 Apr. 2026

Correspondence Address:
More A. L.
Department of Chemistry, BV'S Matoshri Bayabai Shripatrao Kadam Mahavidyalaya, Kadegaon, Dist- Sangli, (MS), India
Email: amolchem1@rediffmail.com

Quick Response Code:

Web. https://csjour.com/

DOI: 10.5281/zenodo.21130709

DOI Link:
https://doi.org/10.5281/zenodo.21130709

Abstract

Transition metal ions such as iron, copper, zinc, manganese, cobalt, and magnesium are involved in numerous physiological functions, including oxygen transport, enzymatic reactions, electron transfer, gene expression, and cellular signalling.[1] Owing to their distinctive electronic structures, variable oxidation states, and flexible coordination behavior, transition metals are particularly vital in biological systems. These properties enable them to participate efficiently in redox processes and complex metabolic pathways.[2] Metals are fundamental to maintaining the structural integrity and functional efficiency of living organisms.[3] Metalloproteins such as haemoglobin, cytochromes, superoxide dismutase, and carbonic anhydrase illustrate the remarkable structural and catalytic versatility conferred by metal cofactors. Through carefully controlled mechanisms of transport, storage, and detoxification, metal ions help preserve cellular homeostasis. However, disturbances in metal ion balance can lead to pathological conditions, including anemia, neurodegenerative diseases, and metabolic disorders. In contrast, non-essential heavy metals may exert toxic effects by interfering with enzymatic systems and promoting oxidative stress.

Recent developments in bioinorganic chemistry have further emphasized the therapeutic and pharmacological potential of metal-based compounds. Transition metal complexes, in particular, have demonstrated significant antimicrobial, anticancer, and anti-inflammatory properties. Therefore, a comprehensive understanding of the biological roles of metals not only clarifies normal physiological processes but also supports the design and development of innovative metal-based therapeutic agents.

Keywords: *Transition metal, enzymatic reactions, metabolic pathways, Metalloproteins.*

Introduction

Metals play a fundamental role in sustaining life. Even though they constitute only a small proportion of total biological matter, their presence is crucial for a wide range of biochemical, structural, and regulatory functions in living organisms.[4] Metals act as enzyme cofactors, maintain the stability of macromolecules, facilitate electron transfer reactions, and regulate gene expression. Maintaining proper metal balance is essential, as both deficiency and excess can disturb homeostasis and contribute to various diseases.[5]

This article examines the biological importance of major transition metals, highlighting their mechanisms of action, pathways of transport and storage, and their relevance to health and disease. Essential transition metals include iron (Fe), copper (Cu), zinc (Zn), manganese (Mn), cobalt (Co), molybdenum (Mo), and nickel (Ni).[6] These elements are key constituents of metalloproteins and metalloenzymes that support vital cellular processes.

For instance:

- Iron is a core component of haemoglobin and cytochromes, where it facilitates oxygen transport and electron transfer.[7]
- Copper functions in oxidative enzymes and participates in redox reactions.
- Zinc contributes to the structural integrity of enzymes and transcription factors.
- Molybdenum plays an important role in nitrogen metabolism.

Bioinorganic chemistry focuses on understanding how metal ions interact with biological ligands such as proteins, nucleic acids, and small biomolecules. Studying these interactions enhances our knowledge of normal physiological functions and provides insight into the molecular basis of metal-related diseases.

(Fig.1) [8]

How to cite this article:
More A. L., Chougule A. M, & Kadam S. S. (2026). Biological Importance of Transition Metals. CompSci Journal, 2(2), 55–61. https://doi.org/10.5281/zenodo.21130709

CompSci Journal
Double Blind Peer Reviewed, Open Access International Research Journal.
ISSN: 3067-3089 Website: https://csjour.com | Volume-2, Issue-2 | April- 2026

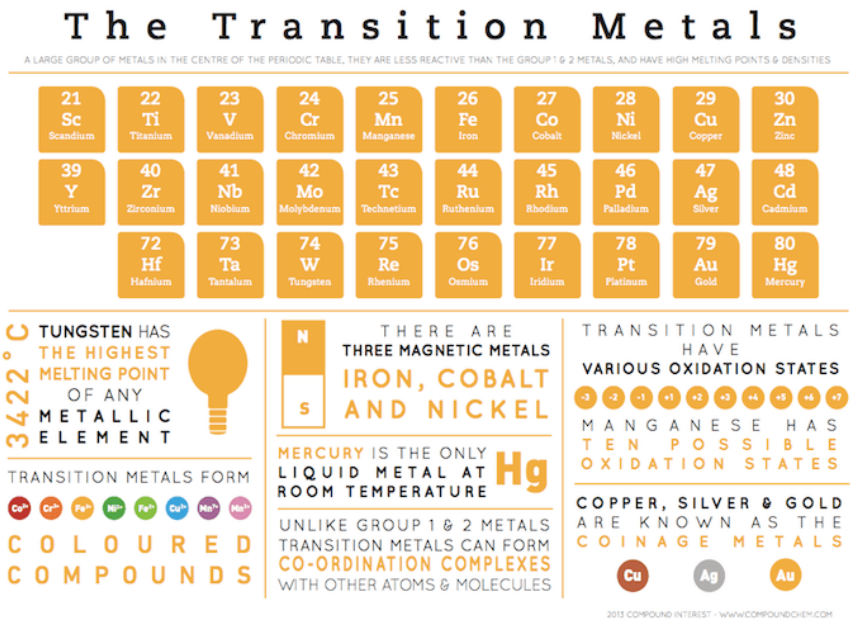

Fig. 1. Biologically relevant transition metals

Classification of Metals in Biology

Biologically relevant metals can be broadly classified into:
Essential metals – required for normal growth, development, and physiology (e.g., Fe, Zn, Cu, Mn, Mg, Ca).
Trace metals – needed in very small amounts but still critical (e.g., Se, Mo, Co).
Non-essential/toxic metals – no known beneficial role and may cause harm (e.g., Pb, Cd, Hg).[9]

Essential Metals:

Iron (Fe):

1. **Biological Role:**

Iron is one of the most abundant and vital metals in biology, serving as a cornerstone for several fundamental life processes. Its role in oxygen transport is perhaps its most well-known function; iron within heme proteins, such as haemoglobin and myoglobin, facilitates the essential binding and movement of oxygen throughout the body.[10] Beyond respiration, iron drives cellular energy production through electron transfer, where iron–sulfur clusters and cytochromes are critical components of the machinery that generates ATP. [11] Furthermore, the metal is indispensable for genetic maintenance and growth, acting as a key cofactor in enzyme catalysis for proteins like ribonucleotide reductase, which is necessary for DNA synthesis.

2. **Homeostasis and Regulation:**

Iron absorption is regulated at the intestinal level via divalent metal transporter 1 (DMT1). The peptide hormone hepcidin controls iron efflux by degrading the ferroprotein transporter, balancing iron levels.

3. **Deficiency and Excess:**

The delicate balance of iron is critical, as both insufficiency and surplus lead to significant clinical complications. Iron deficiency is a global health concern, most commonly manifesting as iron-deficiency anaemia.[12] This condition results in reduced haemoglobin production, causing fatigue, weakness, and impaired physical performance. In children, chronic deficiency is particularly concerning because iron is vital for neurological maturation; its absence can lead to irreversible impaired cognitive development and behavioral issues.

Conversely, iron excess poses a different set of dangers, primarily through a condition known as hereditary hemochromatosis. In this state, the body's regulatory mechanisms fail, leading to massive iron accumulation in organs like the liver, heart, and pancreas, which can result in cirrhosis or heart failure. [13,14]The underlying damage is largely driven by Fenton chemistry, where free iron reacts with hydrogen peroxide to generate highly reactive hydroxyl radicals. These radicals trigger systemic oxidative stress, damaging cellular membranes, proteins, and DNA.

Zinc (Zn):

1. **Biological Role:**

Zinc is a fundamental element that serves as a vital structural and catalytic component in more than 300 enzymes, participating in nearly every major metabolic pathway.[15]Gene expression: Its unique chemical nature as a redox-inert Lewis acid makes it an ideal stabilizer for geneexpression; specifically, zinc-finger proteins utilize Zn^{2+} ions to maintain the structural integrity of loops that bind directly to DNA, thereby regulating the transcription of a vast array of genes. Beyond genomic

control, zinc is indispensable for protein synthesis and cellproliferation, acting as a mandatory cofactor for DNA and RNA polymerases. Zn is essential for lymphocyte activity and cytokine production.

2. Homeostasis:

Unlike iron or calcium, zinc has no specialized storage system in the body, requiring constant dietary intake to maintain levels. Its cellular concentration is precisely managed by ZIP family transporters, which facilitate absorption into the cytoplasm, and ZnT proteins, which handle its export or sequestration. To prevent toxicity and maintain a steady state, metallothionein's bind to ionic zinc, acting as a critical buffer for intracellular zinc levels.

3. Health Implications:

Zinc deficiency primarily targets rapidly dividing cell populations, particularly within the skeletal, integumentary, and immune systems. At the molecular level, zinc is a mandatory cofactor for the synthesis and signaling of **Insulin-like Growth Factor 1 (IGF-1)** and growth hormone.[16] zinc's role in Matrix Metalloproteinases (MMPs)—enzymes that govern tissue remodeling—means that deficiency stalls the inflammatory phase of healing, leading to delayed wound healing and chronic dermatitis.

High intake of zinc induces the synthesis of metallothionein in the intestinal mucosa. This protein has a higher binding affinity for copper than zinc, causing it to sequester dietary copper within enterocytes. Acute ingestion of high doses of zinc (typically exceeding 100–300 mg/day) acts as a direct gastric irritant. This results in the rapid onset of nausea, epigastric pain, vomiting, and abdominal cramps due to the corrosive effect on the gastrointestinal lining.[17]

Copper (Cu):

1. **Biological Role:**

Copper plays a crucial biological role in several essential physiological processes. It functions as a key component of various redox enzymes, including cytochrome c oxidase [18], which is vital for cellular respiration, and superoxide dismutase, which protects cells against oxidative stress through antioxidant defense mechanisms. Copper is also indispensable for connective tissue formation, as the enzyme lysyl oxidase requires copper as a cofactor to catalyze the cross-linking of collagen and elastin. Additionally, copper is involved in neurotransmitter synthesis, contributing to proper nervous system function.

2. **Homeostasis:**

Copper homeostasis is maintained through the coordinated action of specialized transporters and proteins. Cellular copper uptake is primarily mediated by CTR1,[19] while the ATP7A and ATP7B transporters manage its export to prevent toxic accumulation. Once in the bloodstream, copper is bound and transported by ceruloplasmin, ensuring safe delivery throughout the body.

3. **Health Implications:**

Copper deficiency, such as in Menkes disease, leads to severe clinical outcomes including connective tissue defects and progressive neurodegeneration. These symptoms often arise because copper-dependent enzymes cannot function properly without adequate mineral levels.

Copper excess, typically seen in Wilson's disease, results in significant hepatic and neurological damage as a consequence of free radical generation. This oxidative stress occurs when accumulated copper participates in the Fenton reaction, producing toxic hydroxyl radicals that damage cellular lipids, proteins, and DNA.[20]

Magnesium (Mg):

1. Biological Role:

Magnesium is an abundant intracellular cation that plays an essential biological role by stabilizing ATP, as the Mg-ATP complex serves as the actual substrate for most kinases. Furthermore, it acts as a critical cofactor for the activation of over 300 enzymes and is fundamental to maintaining the structural integrity and replication of nucleic acids.

2. Homeostasis:

Magnesium is primarily absorbed in the intestine through a combination of passive paracellular transport and active transcellular pathways.[21] To maintain stable plasma magnesium levels, the kidneys perform efficient renal reabsorption, reclaiming approximately 95% of the filtered magnesium load before it can be excreted in the urine.[22] This tight regulation ensures that magnesium concentrations remain within a narrow physiological range, even as dietary intake fluctuates.

3. Health Implications:

Magnesium deficiency leads to clinical manifestations such as muscle cramps and potentially fatal cardiac **arrhythmias** due to increased neuromuscular excitability. Additionally, low levels can trigger significant metabolic disturbances, often impairing glucose regulation and electrolyte balance.

Magnesium excess, or hypermagnesemia, is a rare condition that generally occurs in the setting of renal impairment, where the kidneys are unable to effectively excrete the mineral. This accumulation can lead to severe complications, including hypotension due to peripheral vasodilation and respiratory depression or paralysis caused by the blockade of neuromuscular transmission. In extreme cases, excessively high magnesium levels can progress to coma and fatal cardiac arrest.

Calcium (Ca):

1. Biological Role:

Calcium serves a fundamental biological role as a primary structural component of bones and teeth, providing the skeletal system with its necessary strength and density.[23] Beyond its structural function, calcium is vital for signal transduction,

acting as a universal second messenger that triggers critical physiological processes such as muscle contraction and neurotransmission. Additionally, it is an indispensable cofactor in the coagulation cascade, facilitating the biochemical reactions essential for blood coagulation.[24]

2. Homeostasis and Regulation:

Calcium homeostasis is precisely controlled by the integrated actions of parathyroid hormone (PTH), calcitonin, and vitamin D, which coordinately regulate absorption and excretion. Although the vast majority of the body's calcium is stored in bone as hydroxyapatite, its blood levels are among the most tightly regulated physiological parameters to ensure constant availability for cellular signalling.

3. Health Implications:

Calcium deficiency can lead to long-term skeletal issues such as osteoporosis, where bones become brittle and prone to fracture, as well as growth retardation in children.[25] Acute deficiency results in tetany, a condition characterized by involuntary muscle spasms and hyperreflexia caused by increased neuromuscular excitability.

Calcium excess leads to hypercalcemia, which can manifest as life-threatening cardiac arrhythmias and the formation of calcium oxalate stones in the urinary tract. [26,27] Furthermore, elevated levels often cause significant neurological issues, ranging from confusion and fatigue to severe cognitive impairment and depression.

Manganese (Mn):

1. **Biological Role:**

Manganese is an essential trace element required for the proper functioning of various metalloenzymes, including arginase, which is vital for amino acid metabolism, and Mn-SOD, the primary antioxidant enzyme in the mitochondria.[28] Beyond its enzymatic roles, manganese is fundamental to healthy bone formation and the regulation of energymetabolism.

2. **Homeostasis:**

Manganese is absorbed via the gut through shared transport pathways with other divalent metals, while its levels are primarily regulated through biliary excretion, with excess manganese being excreted in bile.[29] This hepatic route serves as the main homeostatic mechanism to prevent the accumulation of the metal in systemic circulation and sensitive tissues like the brain.

3. **Health Implications:**

Manganese deficiency is clinically rare due to its presence in many foods, but when it occurs, it can lead to significant skeletal abnormalities and impaired metabolic disturbances.[30] These issues typically arise because the enzymes responsible for bone matrix synthesis and carbohydrate metabolism fail to function without their manganese cofactor.

Manganese excess results in severe neurotoxicity, primarily accumulating in the basal ganglia and manifesting as Parkinsonian symptoms, such as tremors and rigidity. This condition, often referred to as manganism, occurs because elevated manganese levels disrupt dopaminergic signaling and induce oxidative stress within the brain.

Trace Metals:

Selenium (Se), Molybdenum (Mo), Cobalt (Co) are the trace transition metals. They are needed in trace quantity in biological activities.

1. Selenium:

Selenium is a foundational component of selenoproteins, specifically glutathione peroxidases, which serve as a primary defense system to protect cells from oxidative damage.[31] Additionally, it is indispensable for thyroid hormone metabolism, as it facilitates the enzymatic activity of deiodinases required to activate thyroid hormones.

2. Molybdenum:

Molybdenum acts as a vital cofactor for enzymes such as xanthine oxidase and aldehyde oxidase, making it essential for the proper execution of purine metabolism.[32] These molybdenum-dependent enzymes facilitate the final steps of breaking down purines into uric acid, ensuring metabolic waste is processed and excreted correctly.

3. Cobalt:

Cobalt functions as the core structural element of vitamin B12 (cobalamin), which is indispensable for the healthy maturation of red blood cells and the preservation of neurological function. Through its role in B12, cobalt enables essential metabolic processes, including DNA synthesis and the maintenance of the myelin sheath surrounding nerves.[33]

Observation Table: Essential Transition and Group Metals& Trace Metals

Metal	Primary Biological Role	Key Homeostatic Regulators	Clinical Deficiency	Clinical Excess/Toxicity
Iron (Fe)	Oxygen transport (haemoglobin), ATP synthesis, DNA replication	DMT1 (uptake), Hepcidin/Ferroportin (efflux)	Anaemia, fatigue, impaired cognitive development	**Hemochromatosis**, organ failure (liver/heart), ROS damage

Zinc (Zn)	300+ enzymes, gene expression (Zn-fingers), immunity	ZIP (importers), ZnT (exporters), Metallothionein	Stalled wound healing, dermatitis, immune dysfunction	Gastric irritation, **copper/iron deficiency**
Copper (Cu)	Cellular respiration, antioxidant defense, collagen cross-linking	CTR1 (uptake), ATP7A/ATP7B (export)	**Menkes Disease**, neurodegeneration, tissue defects	**Wilson's Disease**, hepatic damage, Fenton reaction toxicity
Magnesium (Mg)	ATP stabilization (Mg-ATP), kinase substrate, DNA replication	Intestinal absorption, renal reabsorption (~95%)	Muscle cramps, arrhythmias, Metabolic disturbances	**Hypermagnesemia**, hypotension, Respiratory depression
Calcium (Ca)	Bone/teeth structure, signal transduction (2nd messenger)	PTH, Vitamin D, Calcitonin	Osteoporosis, **tetany**, growth impediments	**Hypercalcemia**, kidney stones, arrhythmias
Manganese (Mn)	Mitochondrial antioxidant (Mn-SOD), amino acid metabolism	Biliary excretion, SLC30A10 transporter	Rare; skeletal defects, metabolic disturbances	**Manganism** (Parkinsonian symptoms/ neurotoxicity)
Selenium (Se)	Oxidative defense (Glutathione peroxidase), thyroid metabolism	Soil-dependent dietary intake	Oxidative stress, **Keshan disease** (cardiomyopathy)	**Selenosis** (hair/nail loss, neurological damage)
Cobalt (Co)	Essential core of **Vitamin B12 (cobalamin)**	Dietary B12 absorption (Intrinsic factor)	Pernicious anaemia, neurological degeneration	Rare; "Beer drinkers' cardiomyopathy" (historical)
Molybdenum (Mo)	Purine metabolism (Xanthine oxidase), waste processing	Renal excretion	Severe neurological damage (if MoCo deficient)	High uric acid levels (Mimicking gout)

This research is based on a rigorous systematic review of scientific literature, drawing from peer-reviewed journals, foundational textbooks, and authoritative texts in bioinorganic and medicinal chemistry. The methodology followed a structured four-step process:

1. Data Acquisition:
2. Biochemical Evaluation:
3. Pathophysiological Assessment:
4. Clinical Synthesis

Table 2 Essential metal elements to the human body (body weight of Reference Man of 70kg).[34]

Elements	Medium Amount
Fe	5 g
Zn	2 g
Cu	100 mg

Mg	30 g
Ca	1000 g
Mn	16 mg
Mo	5 mg
Co	2 mg
Se	15 mg

Conclusion:

Transition metals—including essential elements such as Fe, Zn, Cu, Mg, Ca, and Mn, and vital trace metals like Se, Mo, and Co—form the indispensable chemical foundation of human physiology. Their unique redox versatility and coordination chemistry enable critical biological functions, from oxygen transport and enzymatic catalysis to antioxidant defense and genomic regulation.

The biological significance of these metals is underscored by the body's requirement for rigorous homeostatic control. As evidenced by disorders like Wilson's disease, Menkes disease, and hereditary hemochromatosis, the margin between life-sustaining necessity and toxic accumulation is narrow. Specialized regulatory systems, such as hepcidin for iron and the ATP7A/B transporters for copper, are essential to preventing the oxidative stress and cellular damage associated with metal imbalance.

Finally, the transition from nutritional essentiality to therapeutic application represents a major frontier in medicinal chemistry. Transition metal complexes are increasingly viewed as promising candidates for antimicrobial and anticancer therapies, highlighting their growing role in drug development. Continued research in bioinorganic chemistry is therefore vital, not only for treating metabolic and genetic disorders but also for pioneering the next generation of targeted molecular medicines.

Acknowledgment

"The authors acknowledge the Department of Chemistry of Dayanand Science College, Latur for providing the facilities and resources necessary to conduct this study".

Financial support and sponsorship

Nil.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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