Herbal Medicine, Radical Scavenger and Metal Detoxification: Bioinorganic, Complexity and Nano Science Perspectives

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Abstract. Developing Complexity Science and Nano Biological perspective giving the ideas of interfacing between modern physical and biological sciences for more comprehensive understanding of life. The study of bioinorganic is a trans-disciplinary, and will initiate the way to more comprehensive and better understanding life. We can talk about energy generation, motive forces and energy transfer at the level of macromolecules. We can then develop understanding biological behavior on nano size biological materials and its higher order using modern physics as well as thermodynamic law. This is a necessity to avoid partial understanding of life that are not match with holism. In animal tissues, the accumulation or overwhelmed production of free radicals can damage cells and are believed to accelerate the progression of cancer, cardiovascular disease, and age-related diseases. Thus a guarded balance of radical species is imperative. Edward Kosower [1] proposed an idea of biradical in an aromatic organic compounds. Each of which having unpaired electrons. The magnetic force of this compound used for making aggregation based on their magnetic characters. Bioinorganic low molecular weight complex compounds composing herbal medicine can bind toxic metals. This low molecular weight complex molecules then easily exerted the metals from the body, removing them from their either intracellular or extracellular existences. This bioinorganic chelation potential is now inspiring a new therapeutic strategies.

Keywords: Bioinorganic-complex compound-scavenger-radicals-intoxication

1. Bioinorganic and Holism Perspectives

Biological system is complex structure with specific function dedicated to perform normal ordered organizational system. Most people are not even conscious that biologists are using what is called the mechanical view of reality when they think and talk. In fact many biological scientists including Medical Science, they still practiced reductionism, reducing things into their parts and examining the parts to understand what made them tick. They reduced life to cells, molecules while the concepts are remaining within Newtonian. In the early 20th Century, the certainty of Newton's mechanics was undermined by quantum mechanics and the Uncertainty Principle developed by Werner Heisenberg . This is the new
challenges to the old Newtonian view of reality. So some biological scientists began abandoning the
Newtonian worldview, while most of them and the ordinary people held on to it.

Developing Complexity Science and Nano Biological perspective are giving the ideas of
interfacing between modern physical and biological sciences for more comprehensive understanding of
life [2,3]. We can then develop understanding biological behavior on nano size biological materials and
its higher order using modern physics as well as thermodynamic law.

In the second half of the 20th century coordination chemistry developed which broadened
understanding of the organic chemical bond to transition metal ions called as bioinorganic complex
compounds [4,5]. The study is commonly called as Bioinorganic Chemistry talking about biochemical
function of “inorganic elements”. The consequence of the works is interdisciplinary research, regarding to
synthesis and analysis of “model systems”. The advantage of Bioinorganic Chemistry is that we can learn
any biochemical process from nature in more holism and original fashion overcoming partial-analytic-
reductive concepts which are normally developed from a test tube in the laboratory.

Figure 1. Evolution of organism along with bioinorganic complex compounds related to energy
generation

The study is very much concerned on control and the use of metal ions in biochemical processes
which are optimized system by evolution (Figure 1), producing efficient system of collection, conversion
and storage of energy. Bioinorganic chemistry is important for the realization of the implications of
electron-transfer proteins, substrate bindings and activation, atom and group transfer chemistry, as well as
metal properties in biological chemistry. Many of them are naturally occurred in biological processes,
such as respiration and photosynthesis [6]. The bioinorganic are metalloproteinase such as Superoxide
Dismutase (SOD), Catalase within mitochondria as well as Hemoglobin in red blood cells and chlorophyll
in leaf cells; they are containing complex organic compounds with metal as central coordinator atom
(Figure 2).

The process system is in mode of moderate conditions processes stand-in by metal proteins. The
main field of research is biological relevant complexes namely biochemistry with metal as center of
coordination chemistry [7]. This will include bio-mineralization namely biochemistry and solid state (materials) chemistry, enzyme which are not dealing with analysis but also synthesis and characterization of model systems by means of computer software. Bioinorganic is a multidisciplinary study and play important roles in understanding regulating combustion, polymerization, and chemical energy transfer processes in physiology. Therefore the characterization of metal ions in biological systems and in particular those bound to proteins has flourished.

**Figure 2.** Bioinorganic, low molecular weight complex with metal as coordinator

The study of bioinorganic is a trans-disciplinary, and will initiate the way to more comprehensive and better understanding life [8]. We can talk about energy generation, motive forces and energy transfer at the level of macromolecules.

**Figure 3.** Bioinorganic is a multidisciplinary study
We can then develop understanding biological behavior on nano size biological materials and its higher order using modern physics as well as thermodynamic law. This is a necessity to avoid partial understanding of life that is not match with holism.

2. Life Process, Nano Size Material, Energy, Bioinorganic and Free Radical Scavenging System

Biological system is complex structure. All sub cellular material such as proteins, DNA, RNA and membranous materials are complex molecular structures which have specific function dedicated to perform ordered organizational system. They are all having functional structure size within 1 to 100 nm. Their behaviors when proceeding life process within the cell are not merely can be thought following Newtonian but also demonstrating electrical and magnetic phenomena. Their intracellular activities are showing their smartness which are following modern physics thoughts.

Life process even though there is a unified basic pattern of life, and we can be more precise and say that this pattern is a network pattern, these networks are not structures — at least most of them — they are functional networks [9]. The energy generation is occurred along with electron transitions amongst atoms which unpaired electron has called as radical (Figure 4). This can be a species of atom or group of atoms (molecule) as gas• that has at least one unpaired electron and is therefore unstable and highly reactive, having rate const. > 10^8 M⁻¹ sec⁻¹.

![Figure 4. Transitional electron. Radical is atom with unpaired electron](image)

Edward Kosower [1] proposed an idea of biradical in an aromatic organic compounds, each of which having unpaired electrons. The magnetic force of this compound used for making aggregation based on their magnetic characters (Figure 5).
Figure 5. Biradical, two atoms with unpaired electron in a compound. This will initiate different type of molecular aggregation.

Metals can play a further role in the design of anion receptors, not as binding centers, but rather as architectural elements. Complex molecules such as DNA, Hemoglobin, chlorophyll, SOD and Catalase plays an important role in scavenging free radicals in life [10]. These compounds have a molecule that binds to the metal. These Metal ions form hydroxyl radicals when it reacts with H₂O₂ through the Haber Weiss or Fenton reaction [1].

Figure 6. TETRACYRROLES. Partially unsaturated tetratentate, macrocyclic ligands. Stable, rigid, planar or nearly planar ring system. Deprotonated forms bind metal ions tightly and size selectively extensive conjugation leads to very intense colors and potentially to redox activity.
The role of radicals in living systems is dual. On the one hand radicals are vital for normal biological functions but on the other hand they are responsible for a variety of deleterious biological processes. In animal tissues, the accumulation or overwhelmed production of free radicals can damage cells and are believed to accelerate the progression of cancer, cardiovascular disease, and age-related diseases. Thus a guarded balance of radical species is imperative. Metal ions have a pronounced tendency to interact with molecules to give structures of varying complexity, which are described by classical coordination chemistry [11].

Bioinorganic compound, namely porphyrin will exhibit differently when they interact with various globins under different exposed pressures as seen in figure 8. Porphyrins are the conjugate acids of ligands that bind metals to form complexes. The metal ions such as Fe, Cu and Mg usually have a charge of 2+ or 3+. A porphyrin without a metal-ion in its cavity is a “free base”. In Hemoglobin and Myoglobin they contain iron-containing porphyrins which are called hemes are found extensively in nature. Hemoglobin and Myoglobin are two O2-binding proteins that contain iron porphyrins. Various Cytochromes and scavenging proteins such as Super Oxide Dismutase and Catalase are also Hemoproteins.

Figure 7. Bioinorganic bind with DNA (upper) and red blood globins (lower)

Iron’s oxidation state in oxyhemoglobin
Assigning oxygenated hemoglobin’s oxidation state is difficult because oxyhemoglobin (Hb-O2), by experimental measurement, is diamagnetic (no net unpaired electrons), and the low-energy electron configurations in both oxygen and iron are paramagnetic (suggesting at least one unpaired electron in the complex).
3. Bioinorganic on Herbal Studies
Herbal medicine use plant or animal materials for medicinal purposes. The study of herbal medicine is often talking about extracted mixing complex compounds. Most of them are remain with their native structures and in the form of complex compounds. Bioinorganic studies using EPR on herbal medicine is shown on figure 7 where extracted fruit flesh and seeds enable to reduce radical of cigarette smoke when observed by EPR Spectroscopic.

Bioinorganic low molecular weight complex compounds composing herbal medicine can bind toxic metals. This low molecular weight complex is molecules then easily excreted the metals from the body, removing them from their either intracellular or extracellular existences. This bioinorganic chelation potential is now inspiring a new therapeutic strategies [12]. The following figure 7 is a theoretical concept of mercury chelation by complex phenanthrene and nicotine contained in tobacco smoke.

Figure 8. The globin behave in diferent ways when it bound with different bioinorganic compounds

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\frac{K_{Mb}}{K_{Hb}} = \frac{[Mb(O_2)]}{[Mb][O_2]} \frac{[Hb(O_2)]^4}{[Hb][O_2]^{2.8}}
\]

Figure 9. The nanostructures of complex molecule characterized by intra spin-spin interaction of the conjugated di-HO•-Phenanthrenediienyl with very mobile electron in their surface.

The mobile electron on surface nanostructure of complex molecule generated by intra spin-spin interaction of the conjugated di-HO•-Phenanthrenediienyl can exhibit electron transition to shade free radicals as shown by their change in their magnetic resonance (Figure 10).
Figure 10. Short-lived free radical observed under EPR Spectroscopy showing free radical shading of Tobacco smoke streamed pass through filter coated by seed extract of \textit{S. cumini}.

4. Instrumentations

The research methodologies to study characteristic of bioinorganic complex compounds of herbal medicinal materials are dealing with analytical techniques aimed to study their natural structures, metal chelating properties, reconstructing their tree dimensional formation as well as evaluating their potential as radical scavenger. Their crystals properties usually showed by the light retardation or birefringence under polarizing microscope, and more specifically observed using X-ray diffraction spectroscopy (XRD). The particles size is measured using Particle Analyzer and observed under Scanning Electron Microscope. The metal components confirm by XRF and SEM. Meanwhile, the LC-MS test can be used to observe the existence of antioxidant compounds with chelating potential to bind transitional metals such as Fe, Cu and Mg forming bioinorganic complex compounds. The paramagnetic properties is observed using Electron Spin Resonance Spectroscopy (ESR). Here is the list of instrumentation needed for bioinorganic characterization:

- Diffraction methods for 3d structure: Problem: crystallization of proteins and Complex structures, “high” resolution (ca. 0.2 nm), no identification of hydrogen atoms
- NMR (Nuclear Magnetic Resonance) for local structure and dynamical properties of species
- Scanning Electron Microscopy (3d structure with medium resolution)
- ESR (Electron Spin Resonance Spectroscopy or EPR (Electron Paramagnetic Resonance) can be used to observe electronic properties of species containing unpaired electrons
- Mössbauer spectroscopy used for identification of species with quadrupol moment
- Optical spectroscopy observing color, birefringence, light retardation
- X-ray absorption techniques for local structure
- SQUID for characterization of magnetic materials
- Cyclovoltammetry for characterization of electron transfer
Acknowledgment

We are very grateful thank to Dr. Gretha Zahar for her valuable suggestions and contribution in developing our understanding on Physical Organic Chemistry. She also kindly let us use her unpublished work namely the nanostructures of complex molecule (Figure 9) for this publication.

References
[1] Kosower EM (1967) An introduction to physical organic chemistry. John Wiley, University of California. USA.
[2] Luisi PL (2006) The Emergence of Life. From Chemical Origins to Synthetic Biology. Cambridge University Press. (http://www.chemiebiologie.unisiegen.de/ac/hjd/lehre/master/bioinorganic_handout.pdf)
[3] Pisani F (2007) Network as a unifying pattern of life involving different process at different levels: An Interview with Fritjof Capra. International Journal of Communication1. Feature 5-25. El Paris-Le Monde-Reforma.
[4] Gray, HB, El Stiefel, J Selverstone Valentine, I Bertini Eds (2006) Biological Inorganic Chemistry: Structure and Reactivity. University Science Books.
[5] Kienle L (2017) Basics of Bioinorganic Chemistry, part 1. Max-Planck-Institut für Festkörperforschun Stuttgart.
[6] Bertini I (ed) (2009) Organic and Bio-inorganic Chemistry. Encyclopedia of Life Support Systems (Vol 1). EOLSS Publishers / UNESCO, Eolss Publishers Co. Ltd., United Kingdom. www.eolss.net.
[7] Brend AH (ed) (2000) Relativistic Effects in Heavy-Element Chemistry and Physics. John Wiley.
[8] Rehder D (2008) Introduction to Bioinorganic Chemistry, Lecture Notes, University of Lund.
[9] Capra F (2007) Complexity and Life in Reframing Complexity: Perspective from the North and South vol. 1 (Capra F., A. Juarrero, P. Sotolongo and J. van Uden eds.). ISCE Publishing, Mansfield, MA. USA.
[10] Albert, B, JD Watson, D Bray, M Raff (2008) Molecular Biology of The Cell. Garland Science, Publishing Co.
[11] Sumitro, SBS, Widyarti, S Permana (2016) Cell Biology. Department of Biology, Brawijaya University.
[12] Swaran JS, and V Pachauri (2010) Chelation in metal Intoxication. Int. J. Environ. Public Health, (7): 2745-2788; doi: 10.3390/ijerph7072745.