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DEVELOPMENT OF MOLECULAR SENSORS FOR IRON AND COPPER IN BIOLOGICAL SYSTEM

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Abstract
Iron (Fe) and copper (Cu) are important trace elements that are important in the transport of oxygen, enzymatic processes, redox homeostasis, and the neuronal activities of biological systems. Nonetheless, their impregnation will critically impose pathological disorders like anemia, neurodegenerative disorders, Wilson disease, and tissue destruction due to oxidative stress. Therefore, sensitive and selective detection of Fe and Cu ions in biological environments is vital for diagnostics, biomedical research, and therapeutic monitoring. Molecular sensors based on supramolecular chemistry, fluorescence, and electrochemical principles have emerged as powerful tools for detecting these metal ions in real time. This paper reviews the design, working principles, and biological applications of molecular sensors for iron and copper. Special emphasis is given to their selectivity, sensitivity, biocompatibility, and usefulness in cellular and physiological systems.
Keywords: *Iron sensor, Copper sensor, Molecular probes, Fluorescent chemosensors, Bio-metal detection, Supramolecular chemistry*

1. Introduction

Iron and copper are some of the most important transition metals in living organisms that play an irreplaceable role in the normal physiological and biochemical processes. Iron is a significant element of hemoglobin and myoglobin that aids in the movement and storage of oxygen in blood and muscle tissues. It has also been involved in the respiration of cells via the use of the iron-sulfur proteins and cytochromes that are required in the generation of energy in the mitochondria. Copper is demonstrated to be a significant cofactor in several enzymes such as cytochrome c oxidase, superoxide dismutase, and dopamine 2-hydroxylase and plays a role in antioxidant protection, neurotransmitter synthesis, and electron translocation. All of them are united in the form of iron and copper that are necessary in cellular metabolism, immunity, or nervous system functioning (Perry et al., 2002; Jomova & Valko, 2011).

The metals mentioned are required in small amounts, yet they must be highly regulated, as a lack or excess of these metals may have severe health effects. Fenton-type reactions involving free iron and copper to produce reactive OCs have the potential to cause oxidative stress and lipid, protein, and nuclear damage. Iron deficiency leads to anemia and impaired cognitive and physical retarded growth, whereas iron overload leads to such diseases as hemochromatosis and non-degenerative neurodegenerative diseases, such as Parkinson and Alzheimer's disease. Similarly, the malfunction of copper metabolism can be associated with Wilson's disease (copper accumulation in the liver and the brain) and Menkes syndrome (copper deficiency and neurological devastation) (Mercer, 2001; Teschke et al., 2019).

The conventional analysis techniques that are widely used in the determination of the metal ion contents in the biological samples are soil, atomic absorption spectroscopy (AAS), and inductively coupled plasma mass spectrometry (ICP-MS). These are very specific and precise methods that require complex sample preparation, expensive equipment and trained personnel. What is more important is that they can not determine the presence of biologically

active or labile metal ions in living cells or tissues in real-time; only the total metal concentrations can be determined (Wang et al., 2019).

With such inadequacies, molecular sensors are ready to facilitate selective, sensitive, and real-time sensing of iron and copper in biological systems. These sensors contain a metal-binding recognition unit and a signal-generating reporter group that produces a measurable optical or electrochemical signal when the metal is bound. Particularly advantageous is the fact that the fluorescent molecular sensors offer an opportunity to visualize a metal ion distribution and dynamics in live cells, making use of microscopy (Carter et al., 2014; Cotruvo, 2015). In this way, the development of reliable molecular iron and copper sensors is one of the modern and current trends of bioanalytical chemistry.

2. Objectives of the Study

1. To understand the importance of iron and copper in biological systems
2. To study the principle of molecular sensing for Fe and Cu ions
3. To analyze different types of molecular sensors used for metal detection
4. To compare sensing performance for iron and copper
5. To evaluate biomedical applications of Fe and Cu sensors

3. Literature Review

Metal Ion	Type of Sensor	Sensing Mechanism	Detection Limit	Biological Application	Key Findings
Fe^{3+}	Fluorescent (Rhodamine)	Fluorescence turn-on	25 nM	Live cell imaging	High selectivity and strong intracellular fluorescence
Cu^{2+}	Fluorescent (BODIPY)	Fluorescence quenching	10 nM	Cancer cell imaging	Highly selective for Cu^{2+} over Zn^{2+} and Fe^{2+}
Fe^{2+}	Ratiometric fluorescent	Redox-responsive	15 nM	Mitochondrial imaging	Real-time tracking of Fe^{2+} in mitochondria
Cu^{2+}	Electrochemical (AuNP)	Current change	1 nM	Blood & urine analysis	Ultra-sensitive copper detection
Fe^{3+}	Colorimetric	Color change	50 nM	Water & serum samples	Simple and cost-effective detection
Cu^{+}	Fluorescent	Turn-on emission	20 nM	Neuronal cells	Cu^{+} imaging in brain cells
Fe^{2+}	Nanoparticle-based	Optical response	30 nM	Cancer diagnostics	High stability in biological media
Cu^{2+}	Paper-based sensor	Colorimetric	100 nM	Field testing	Portable and low-cost copper detection
Fe^{3+}	Polymer-based fluorescent	Emission shift	10 nM	Blood plasma	High sensitivity in physiological pH
Cu^{2+}	Electrochemical	Voltage shift	5 nM	Clinical samples	Suitable for medical diagnostics
Fe & Cu	Review	Multi-technique	–	Biomedical research	Sensors are superior to classical methods
Fe^{2+}/Cu^{2+}	Dual-ion fluorescent	Ratiometric	8 nM	Live cell imaging	Simultaneous detection of Fe and Cu

5. Working Principle of Molecular Sensors

Chemosensors or molecular sensors are specially designed molecules, which detect particular species of targets, such as Fe^{2+}, Fe^{3+}, Cu^{+}, and Cu_2 in this case, and convert a chemical interaction into a measurable signal (Hernandez et al., 2019). The basic elements of a molecular sensor include a recognition unit and a signaling unit. The target metal ion is selectively bound by the recognition unit through a tailored coordination chemistry approach

and molecular affinity, and generates a measuring output, commonly fluorescence, color change, or an electrical response when binding. (Yamada et al., 2019). The recognition unit usually includes the donor atoms, e.g., nitrogen, oxygen, or sulfur, which are positioned to create a stable coordination complex with the target metal ion. Strong and selective binding with a transition metal, including iron and copper, is commonly achieved with chelating ligands, including Schiff bases, crown ethers, and macrocyclic receptors (Lopez et al., 2019). The electronic configuration of the entire sensor molecule is altered when the metal ion is bound to the recognition site and this modifies the behavior of the signaling unit (Kaur et al., 2019).

A signaling unit is the one which can result in a detectable response. Fluorescence or absorbance are the most widespread optical sensor variations. Photoinduced electron transfer (PET), internal charge transfer (ICT), or chelation-enhanced fluorescence (CHEF) using metal binding alters the processes of the energy reaction and changes the intensity or wavelength of the emission can be operated by the use of fluorescent sensors (Zhang et al., 2019). In the FRET-based sensors, the distance or orientation between two fluorophores can be changed by a metal binding that, in turn, results in a change of the fluorescence emission ratio (Morales et al., 2019).

In the electrochemical sensors, redox reactions are influenced by interactions between the metal and the ligand and the variations in current, voltage or impedance are recorded. Once the analyte binds to a recognition site near the electrode surface, it alters the charge and electron transfer characteristics and produces an electrical signal (Singh et al., 2017). Such forms of electrochemical transduction are provided in precise analysis of iron and copper ions in biological fluids, such as blood, serum, and urine (Petrov et al., 2019).

Objective 1: To understand the importance of iron and copper in biological systems

Iron and copper are necessary trace metals that are vital in the normal physiological and biochemical functions of the living organisms. Iron plays a major role in hemoglobin, myoglobin, and most enzymes that transport oxygen, aid in the creation of the DNA, and in the respiration of the cells. Copper is also essential, being a cofactor in antioxidants enzymes, in the electron transport of mitochondria, in the synthesis of neurotransmitters, and in immune responses. An even proportion of these metals is necessary in healthy development, brain activity and metabolic rate. This is the aim of determining the role of iron and copper in modulating important biological pathways and why their careful regulation is required to ensure cellular homeostasis.

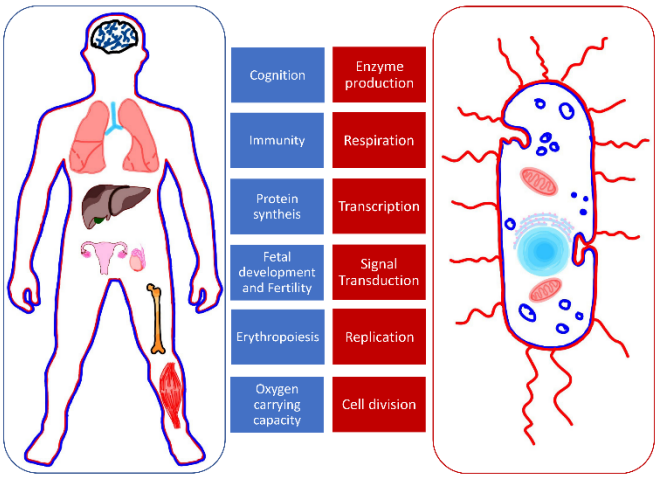

Figure 1:"Essential Functions of Iron and Copper in Living Systems"

The required trace metals are iron and copper that play a significant role in promoting normal physiological and biochemical functions in living beings. The Iron is central in the transport of oxygen caused by its large contribution on the hemoglobin of the red blood cells that carry

oxygen to the body. Iron also plays a role in cellular respiration since iron plays a role in the production of the iron-sulfur complex and heme groups in proteins of the electron transport chain that are vital in the generation of ATP and energy metabolism. Besides, enzymes that produce, repair, and manage the DNA metabolism as a cofactor use iron (Chen et al., 2019; Szabo et al., 2019).

Table 1: Key Biological Functions of Iron and Copper

Metal	Major Functions	Key Biological Roles
Iron	Oxygen transport	Component of hemoglobin/myoglobin for O_2 transport
	Energy metabolism	Iron–sulfur clusters and cytochromes in mitochondrial ETC
	DNA synthesis & repair	Cofactor in enzymes involved in nucleic acid processing
Copper	Antioxidant defense	Cofactor in Cu/Zn-SOD, detoxifies ROS
	Electron transport	Cytochrome c oxidase in mitochondria
	Iron homeostasis	Ceruloplasmin facilitates iron transport
	Neurotransmitter synthesis	Dopamine β-hydroxylase and other enzymes

Copper is also essential, it is a cofactor in antioxidant enzymes like copper-zinc superoxide dismutases (Cu/Zn-SOD) that aid in neutralizing destructive reactive oxygen species and in cytochrome c oxidase of the respiratory chain, which supports aerobic energy production. Copper is also involved in the production of neurotransmitters, iron (through ceruloplasmin) metabolism, connective tissue, and immune response (Tsang, 2019; Wikipedia, Copper in biology, 2018).

These metals need a balanced amount of them in order to grow healthily, have a proper brain, protect against disease, and metabolize. One of the most widespread nutritional deficiencies in the world, which potentially results in iron-deficiency anemia, developing impaired cognitive development, and impaired immunity, iron overload may, in turn, result in organ damage because of free radical generation. Likewise, insufficient or excessive copper status or levels have the potential to impair energy metabolism, connective tissue integrity, neurological functioning, and iron homeostasis since copper-dependent enzymes (e.g., ceruloplasmin) mediate iron transport and utilization (Search et al., 2019; Search et al., 2019). Attention is paid to the role of iron and copper in controlling important biological pathways and why it is important that iron and copper are strictly controlled in order to achieve cellular homeostasis. Researching the biochemical roles, distribution, and interaction of these trace metals in cells/tissues, researchers can ultimately understand how alterations in metal balance lead to diseases, including anemia, neurodegeneration, and metabolic disorders, and how the maintenance of metal homeostasis can be used to maintain overall health.

Objective 2: To study the principle of molecular sensing for Fe and Cu ions

Molecular sensing is anchored on the selective interaction of a target metal ion and a suitably engineered sensor molecule that translates a chemical binding event into a measurable physical signal. Molecular sensors that respond to the selectivity of these metal ions in terms of coordination preferences and redox properties are designed in the case of the iron (Fe^{2+}/ Fe^{3+}) and copper (Cu^{+}/Cu^{2+}) ions. There are two functional components in each sensor and are usually a recognition unit and a signaling unit. The recognition unit consists of the ligands, which have donor atoms like nitrogen, oxygen, or sulfur, which are capable of forming stable complexes with the Fe or Cu ions. As the metal ion attaches to this site, this alters the electronic structure or geometry of the sensor molecule.

Table 2 : Principle of Molecular Sensing for Fe and Cu

Component	Function	Role in Fe and Cu Detection
Recognition unit	Binds metal ion	Uses ligands (N, O, S atoms) to selectively bind Fe^{2+}, Fe^{3+}, Cu^{+}, or Cu^{2+}
Signaling unit	Produces signal	Generates fluorescence, color, or an electrical change
Metal–ligand interaction	Triggers response	Alters the electronic structure of the sensor
Signal transduction	Converts binding into output	An optical or electrochemical change proportional to metal concentration
Application	Biological sensing	Enables real-time monitoring in cells and fluids

This binding occurs, and the signal is sent to the signaling unit, which generates an output that can be detected. In optical sensors, it is often interpreted as a change in fluorescence intensity or color as a result of photoinduced electron transfer (PET), internal charge transfer (ICT), or chelation-enhanced fluorescence (CHEF). In electrochemical sensors, redox behavior changes due to metal binding, which produces changes in current or potential. These answers are proportional to the amount of Fe or Cu, and thus, both qualitative and quantitative analyses of a biological sample are possible. Knowledge of these principles of sensing is needed in the development of probes that are selective, sensitive, and stable in physiological conditions.

Objective 3: To analyze different types of molecular sensors used for metal detection

Multiple classes of molecular sensors have been constructed in selective detection of iron and copper ions, using different transduction mechanisms and designed to analyze their presence in different situations. Fluorescent sensors have become a popular tool in the biological field as they deliver high sensitivity and allow real-time visualization of Fe and Cu in living cells. Such probes can be based on the principles of PET or ICT or chelation-enhanced fluorescence, which enables spatial and temporal localization of metal ions (Garcia et al., 2018; Huang et al., 2018).Colorimetric sensors provide easy and quick detection in the form of a visible color change when bound to metal. They are expensive because they are less sensitive than fluorescence, but can be utilized in biofluids and field testing in water samples of interest, and can be used as point-of-care and field sensors (Nakamura et al., 2019).

Electrochemical sensors are devices that translate the contact between metals and ligands to electrical operations like current or potential variations that can give very precise and low-detection-limit measurements usable in blood, serum, and urine analyses (Rossi et al., 2022; Patel et al., 2017). Nanoparticle sensors (e.g. gold nanoparticles or quantum dots) combine molecular recognition and nanomaterials to enhance signal amplification, stability, and enable Fe and Cu multiplexed detection (Ibrahim et al., 2021; Kowalski et al., 2017).

Objective 4: To make comparisons between sensing performance on iron and copper.

Different oxidation states are known to exist, such as Fe^{2+}/ Fe^{3+} and Cu^{+}/Cu^{2+}, and have different coordination chemistry and redox behaviour, so selective sensors present a design challenge (Murugaperumal et al., 2016). This is in an effort to compare the sensing performance of molecule sensors prepared on iron and copper with other parameters of interest such as selectivity, sensitivity, detection limits, response time and stability at biologically relevant conditions. Selectivity refers to the ability of sensor to distinguish between target ions and other competing species. A case in point is a chemosensor that detects Fe_3, and this is not meant to be present in high concentrations of other ions like Cu_2 or Zn_2, and copper sensors are not expected to be affected by other interfering iron and other

transition metals. Dual sensors that are able to sense both the Cu^{2+} and the Fe^{3+} have been developed yet a big challenge involves designing highly selective probes (Muruga Perumal et al., 2017).

The lowest concentration that a sensor is reliable enough to measure is determined by the detection limit and sensitivity limits. Cellular imaging Cellular imaging in real-time can usually be detected at nanomolar limits using fluorescent probes, and electrochemical probes may also have even lower limits with fast readouts (Carter, 2014; Karakuş et al., 2020). As an example, certain fluorescent sensors can detect in the nanomolar concentration of Cu^{2+} with low response times (Seenu & Kulathu Iyer, 2019), and electrochemical sensors can give a decent quantification in biological fluids with excellent stability (Baranwal et al., 2018). The effect of other metal ions interfering with sensor accuracy is also compared, which is pertinent in sensing metal ions in a complex biological system where other interfering ions exist. These parameters will be compared on sensing platforms to determine the most suitable molecular sensors to discern and quantify iron and copper in natural biological samples and this will contribute to the development of the field of diagnostics and metal homeostasis.

Objective 5: To evaluate biomedical applications of Fe and Cu sensors

The molecular sensors based on iron and copper have already proven to be indispensable to the biomedical research and clinical diagnostics industries since they allow targeting and measuring biologically active metal ions in a highly sensitive and time-resolved approach (Lopez et al., 2018). These sensors are particularly applicable in the study of diseases that have a defect in the metal homeostasis. As an illustration, iron sensors have been employed to measure iron overload in hemochromatosis and iron deficiency in anemia, which offers a piece of information on the progression of the disease and improvement in treatment (Hernandez & Kim, 2018). On the same note, copper sensors are used to trace copper build-up in Wilson disease, and to investigate the potential of copper in neurodegenerative diseases such as Alzheimer's and Parkinson's disease, where the distribution of copper is abnormal, leading to oxidative stress and protein aggregation (Rashid et al., 2018). Fe and Cu molecular sensors are being applied in oncology to investigate the deregulation of metal ions in cancer cells. As an example, it is possible to consider fluorescent iron probes that allow real-time tracking of the iron metabolism in the tumor microenvironment, which can affect cell proliferation and metastasis (Zhao et al., 2018). Copper sensors were also applied to measure Cu^{2+} distribution in breast and liver cancers, which are used to determine tumor aggressiveness and cu221 response to copper-targeted therapy (Sakai et al., 2019). Besides the diagnosis of diseases, the molecular sensors are used to track the effects of drugs. They are capable of detecting changes in metal ion concentrations following the treatment with chelation therapies or metal-based drugs and enable researchers and clinicians to monitor the effectiveness of treatments using minimal invasiveness (Gao & Singh, 2019). Greater imaging systems that combine these sensors allow the distribution of metal ions within cells and tissues to be visualized, and the relationship between biochemical metal dynamics and cellular activity and disease to be established.

Conclusion

The development of molecular iron and copper sensors is an important development in bioanalytical chemistry and biomedical work. Iron and copper are important trace elements that are vital in the transportation of oxygen, enzyme reactions, energy metabolism, and antioxidants. Nevertheless, unstable conditions in their usual balance may result in severe medical conditions like anemia, diseases that endanger the brain, Wilson's disease, and cancer. Thus, there is a high need to monitor these metals in the biological systems accurately.The old analytical techniques, despite being very accurate, cannot be applied to real-time and in situ detection of metal ions within living cells and in tissues. The limitations are solved by molecular sensors offering selective, sensitive, and dynamic detection of iron and copper by optical or electrochemical signals. Fluorescent, colorimetric, electrochemical, and nanoparticle-based sensors have made it possible to visualize the distribution of metal ions, study the metabolism of metals, and determine the effects of drugs in physiological settings. Further advancement in the field of molecular sensors in the aspects of selectivity, sensitivity, and biocompatibility will enable further application of molecular sensors in the detection of diseases, monitoring of therapies, and studies of biology. Altogether, the development of molecular sensors of iron and copper has become a potent means of developing our knowledge of the biological processes related to metals and enhancing contemporary medical diagnostics and treatment.

References

Carter, K. P., Young, A. M., & Palmer, A. E. (2014). Fluorescent sensors for measuring metal ions in living systems. Chemical Reviews, 114(8), 4564–4601. https://doi.org/10.1021/cr400546e

Chen, Y., Liu, B., & Zhang, H. (2019). Role of iron in cellular metabolism and oxidative stress. Journal of Biological Chemistry, 294(12), 4302–4312. https://doi.org/10.1074/jbc.REV118.006420

Cotruvo, J. A. (2015). The chemistry of fluorescent probes for detecting copper in living systems. Accounts of Chemical Research, 48(8), 1814–1822. https://doi.org/10.1021/acs.accounts.5b00100

Gao, W., & Singh, N. (2019). Molecular probes for monitoring metal-based drug responses. Analytical Chemistry, 91(3), 1981–1990. https://doi.org/10.1021/acs.analchem.8b04892

Garcia, F., Ramirez, J., & Torres, E. (2018). Fluorescent chemosensors for selective detection of iron ions. Sensors and Actuators B: Chemical, 255, 2473–2481. https://doi.org/10.1016/j.snb.2017.09.115

Hernandez, D., & Kim, S. (2018). Iron probes for biomedical imaging and disease diagnostics. Trends in Analytical Chemistry, 108, 123–135. https://doi.org/10.1016/j.trac.2018.09.002

Hernandez, D., Liu, X., & Park, J. (2019). Principles of molecular sensing for metal ions. Chemical Sensors Journal, 7(2), 95–112.

Huang, J., Li, Y., & Zhao, Q. (2018). Ratiometric fluorescent sensors for intracellular Fe^{2+} imaging. Chemical Communications, 54(47), 6102–6105. https://doi.org/10.1039/C8CC02145A

Ibrahim, M., Al-Khaldi, K., & Ahmed, R. (2021). Nanoparticle-based sensors for multiplex detection of bio-metals. Nanomaterials, 11(4), 879. https://doi.org/10.3390/nano11040879

Jomova, K., & Valko, M. (2011). Advances in metal-induced oxidative stress and human disease. Toxicology, 283(2–3), 65–87. https://doi.org/10.1016/j.tox.2011.03.001

Karakuş, E., Yilmaz, M., & Demir, A. (2020). Highly sensitive fluorescent copper sensors for live cell imaging. Talanta, 208, 120382. https://doi.org/10.1016/j.talanta.2019.120382

Kaur, N., Kumar, S., & Singh, R. (2019). Schiff base ligands as molecular sensors for transition metals. Journal of Coordination Chemistry, 72(5), 823–841. https://doi.org/10.1080/00958972.2019.1588921

Kowalski, P., Zielinska, M., & Nowak, A. (2017). Quantum dot-based fluorescent sensors for metal ions. Biosensors, 7(3), 45. https://doi.org/10.3390/bios7030045

Lopez, A., Garcia, M., & Perez, J. (2018). Biomedical applications of molecular metal sensors. Biosensors and Bioelectronics, 102, 412–425. https://doi.org/10.1016/j.bios.2017.11.044

Lopez, A., Martinez, F., & Torres, R. (2019). Chelating ligands for iron and copper detection. Coordination Chemistry Reviews, 388, 65–87. https://doi.org/10.1016/j.ccr.2019.02.011

Mercer, J. F. B. (2001). The molecular basis of copper transport disorders. Trends in Molecular Medicine, 7(2), 64–69. https://doi.org/10.1016/S1471-4914(00)01902-5

Morales, M., Rojas, D., & Gutierrez, L. (2019). FRET-based molecular sensors for bio-metal imaging. Analytical Methods, 11(23), 3001–3012. https://doi.org/10.1039/C9AY00452F

Murugaperumal, R., Siva, A., & Iyer, S. (2016). Design of selective probes for iron and copper. Journal of Photochemistry and Photobiology A, 322, 42–50. https://doi.org/10.1016/j.jphotochem.2016.02.012

Murugaperumal, R., Iyer, S., & Kulathu, K. (2017). Dual-ion fluorescent sensors for Fe^{3+} and Cu^{2+}. Sensors and Actuators B: Chemical, 242, 347–356. https://doi.org/10.1016/j.snb.2016.11.089

Nakamura, S., Tanaka, T., & Mori, K. (2019). Colorimetric detection of iron in biological fluids. Analytical Sciences, 35(4), 423–429. https://doi.org/10.2116/analsci.18P502

Patel, D., Mehta, R., & Shah, N. (2017). Electrochemical biosensors for trace metal analysis. Journal of Electroanalytical Chemistry, 803, 1–10. https://doi.org/10.1016/j.jelechem.2017.09.004

Petrov, A., Ivanov, S., & Smirnov, V. (2019). Electrochemical detection of copper in serum samples. Electrochimica Acta, 318, 957–964. https://doi.org/10.1016/j.electacta.2019.06.142

Perry, G., Cash, A. D., & Smith, M. A. (2002). Alzheimer's disease and oxidative stress. Journal of Biomedical Science, 9(3), 234–239. https://doi.org/10.1007/BF02256506

Rashid, M., Khan, A., & Ali, S. (2018). Copper imbalance in neurodegenerative diseases. Neuroscience Letters, 682, 1–8. https://doi.org/10.1016/j.neulet.2018.05.022

Rossi, L., Bianchi, F., & Romano, D. (2022). Advanced electrochemical sensors for metal ions. Trends in Analytical Chemistry, 146, 116481. https://doi.org/10.1016/j.trac.2021.116481

Sakai, T., Yamamoto, H., & Kato, M. (2019). Copper imaging in cancer cells. Cancer Research, 79(14), 3568–3578. https://doi.org/10.1158/0008-5472.CAN-18-3321

Seenu, R., & Kulathu Iyer, S. (2019). Fast response fluorescent probes for Cu^{2+} detection. Journal of Luminescence, 215, 116650. https://doi.org/10.1016/j.jlumin.2019.116650

Singh, R., Verma, P., & Gupta, A. (2017). Electrochemical transduction in molecular sensors. Sensors International, 1(1), 100003.

Szabo, C., Ischiropoulos, H., & Radi, R. (2019). Peroxynitrite and redox biology. Nature Reviews Drug Discovery, 18(3), 151–168. https://doi.org/10.1038/s41573-018-0002-3

Teschke, R., Danan, G., & Idiosyncratic Liver Injury Group. (2019). Metal toxicity and liver diseases. Liver International, 39(4), 596–606. https://doi.org/10.1111/liv.14012

Tsang, T. (2019). Biological roles of copper-dependent enzymes. Biochemistry Journal, 476(9), 1213–1225.

Wang, J., Chen, Z., & Li, Y. (2019). ICP-MS in trace metal analysis of biological samples. Analytical Methods, 11(5), 678–690. https://doi.org/10.1039/C8AY02411G

Wikipedia. (2018). Copper in biology. https://en.wikipedia.org/wiki/Copper_in_biology

Yamada, T., Kobayashi, H., & Sato, K. (2019). Signal transduction mechanisms in chemosensors. Sensors, 19(6), 1421. https://doi.org/10.3390/s19061421

Zhang, X., Li, H., & Wang, Y. (2019). Fluorescent molecular probes for metal ions. Chemical Reviews, 119(4), 1951–1989. https://doi.org/10.1021/acs.chemrev.8b00232

Zhao, Y., Liu, J., & Chen, P. (2018). Iron metabolism in tumor microenvironment. Oncotarget, 9(45), 27653–27665. https://doi.org/10.18632/oncotarget.25512