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Biological Applications of Transition Metal Complexes of Schiff Bases containing Thiosemicarbazone: A Review

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Abstract: *Transition metal complexes of Schiff base containing thiosemicarbazone have appeared as a vital class of biologically active compounds in bioinorganic and medicinal chemistry which have therapeutic potential in the treatment of microbial infections, parasitic diseases, cancer disease and other pathological conditions. These ligands exhibit significant coordination ability because of the presence of nitrogen and sulphur as donor atoms. When these ligands are coordinated with transition metals, the chelation enhances their biological activities and the resulting complexes exhibit pharmacological effects which make them promising candidates in medicinal chemistry. The characteristics of these complexes such as redox behaviour, various coordination geometries and strong interactions with biomolecules make them to interact selectively with the biological targets. The present review provides the current knowledge on structural activity relationships, coordination behaviour, biological applications and toxicological considerations of transition metal complexes of thiosemicarbazone Schiff bases. The review also emphasizes on antibacterial, antifungal, antiviral, antioxidant and anticancer activities and future research directions in inorganic medicinal chemistry.*

Keywords: *Thiosemicarbazone, Schiff bases, Biological activity, Biological active compounds, medicinal chemistry, pharmacological effects*

I. INTRODUCTION

Hugo Schiff (1864) proposed an important class of chemical compounds which are imine derivatives formed by the condensation of primary amines with carbonyl compounds such as aldehydes and ketones. Schiff bases act as ligand that forms a variety of coordination complexes with metal ions by coordinating through azomethine or imine (>C=N–) group. When thiosemicarbazide as the amine component, combines with the carbonyl compounds, Schiff bases are formed which are known as thiosemicarbazone. The thiosemicarbazone ligands consist of sulphur of carbonyl group and nitrogen of azomethine group as donor atoms. These ligands exhibit the ability to exist in different tautomeric forms, particularly in thiosemicarbazones, which exist in both thione and thiol forms. This tautomerism plays an important role in binding of the ligand with metal ions. In many cases, deprotonation of ligand occurs during the complex formation which leads to stronger metal – ligand bonding and greater stability of the resulting complex. Such versatility in the bonding offers chemists the opportunity to design and control the properties of metal complexes for specific applications. Therefore, researchers suggest the applications of metal complexes of thiosemicarbazone in various fields of bioinorganic chemistry, biomedical sciences and material sciences in addition to coordination chemistry [1]. The Schiff base transition metal complexes also have wide applications in agricultural activities, catalysis, polymer, dyes and pharmaceutical industries. Schiff bases derived from thiosemicarbazone have attracted more attention over the years among various ligands because of their ease of synthesis, versatile coordinating characteristics and having wide range of biologically active metal complexes. The Schiff base ligands of thiosemicarbazone possess an ability to bind effectively with transition metal ions through multiple donor atoms such as nitrogen, sulphur and other substituted atoms. The special multidentate characteristic of such type of ligands makes them excellent chelating agents to form mononuclear complexes and more complex polynuclear systems. Transition metals such as copper, cobalt, nickel, iron, zinc, manganese etc. form stable coordination complexes with these ligands [3]. These characteristics of coordination allow the metal complexes to participate in biological redox reactions and interact with the biomolecules such as enzymes, proteins and DNA. In the recent years, the development of metal based drugs has gained greater importance in the field of bioinorganic chemistry. Researchers have reported antibacterial, antifungal, antioxidant, analgesic, antipyretic, antidiabetic, antimalarial and anticancer properties of such metal complexes [2].

The present review focuses on the literature related to various biological applications of transition metal complexes of Schiff bases derived from thiosemicarbazone, suggesting the possibilities of these complexes in the pharmaceutical and medicinal fields.

II. SYNTHESIS AND COORDINATION CHEMISTRY:

2.1 General Synthesis of Schiff Base Ligand:

Schiff bases of thiosemicarbazones are synthesized by the condensation reaction between carbonyl compounds with thiosemicarbazide in a suitable organic solvent such as ethanol in distilled form under reflux. The Schiff base thiosemicarbazone ligands contain sulphur and nitrogen atoms which make them suitable for the formation of stable complexes with the metal ions. It exhibits thione – thiol tautomerism which allows the ligand can coordinate through nitrogen and sulphur atoms, forming the chelate rings with transition metal ions. The presence of sulphur increases their ability to coordinate with metal ions and also increases their biological activity. Depending on the structure of these ligands, they generally act as bidentate, tridentate or even polydentate ligands [3, 4].

2.2 Synthesis of Metal Complexes:

The synthesis of metal complexes involves the mixing of the Schiff base ligand with a suitable metal salt in a coordinating solvent such as methanol, ethanol or dimethylformamide under controlled conditions. The parameters such as pH, temperature and metal – ligand ratio play an important role in determining the structure of the metal complex. The process of complexation is carried out at high temperature with pH adjustment by using bases like sodium hydroxide and potassium hydroxide for chelation. Isolation of metal complexes is achieved by filtration and recrystallization [5, 6].

2.3 Coordination Chemistry of Transition Metal Complexes:

The coordination behaviour depends on the factors such as reaction conditions, nature of the metal ions, type of ligand, presence of substituents in ligand etc. In addition, chelation enhances the stability and affects their physicochemical and biological characteristics. The nature of substituent attached with the Schiff base ligand can also affect the ligand field strength, metal – ligand bond character and the stability of metal complex which in turn affects biological activity [4].

Transition metal complexes of thiosemicarbazones exhibit various types of coordination stereochemistry around the metal ions such as octahedral, square planar, tetrahedral etc. Copper (II) complexes exhibits square planar or distorted square pyramidal geometries, nickel (II) complexes show square planar or octahedral while cobalt (II) and zinc (II) can display both tetrahedral and octahedral geometries. The common techniques used for characterization of metal complexes include infrared spectroscopy, nuclear magnetic resonance, UV – visible spectroscopy, X – ray crystallography, magnetic susceptibility measurements etc. These techniques help to establish the metal – ligand coordination mode, geometry and electronic properties of the metal complexes [7, 8].

III. BIOLOGICAL APPLICATIONS:

3.1 Antibacterial Activity:

The antimicrobial activity is one of the most important biological applications of the metal complexes. Transition metal complexes of thiosemicarbazones exhibit strong antibacterial and antifungal effects against various pathogens. Various studies have shown that the metal complexes exhibits enhanced activity than the parent ligand which can be explained by the chelation theory. Chelation reduces the polarity of the metal ion and increases the lipophilicity which allows the complex to penetrate microbial cell membranes more effectively. Various researchers reported that copper (II) and cobalt

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(II) complexes of thiosemicarbazones exhibit strong activity against various bacteria such as *Escherichia coli Aspergillus niger, Staphylococcus aureus* etc., while nickel (II) and zinc (II) complexes with these ligands show moderate antibacterial activity. Moreover, several researchers have been observed that cobalt (II) complexes are more effective against both Gram-positive and Gram-negative bacteria due to interactions with bacterial DNA and membrane disruption. Rakhi and Shelly (2011) reported the antibacterial activity of coordination complexes of copper (II), nickel (II) and cobalt (II) with 2,5-Dihydroxy butyrophenone thiosemicarbazone and 2,5-Dihydroxy bezophenone thiosemicarbazone as primary ligand and 2,2'-bipyridyl as secondary ligand against pathogenic bacteria *E. Coli, S. aureus, B. megaterium* and *B. cereus*. They observed that greater activity of mixed complexes compared to the metal salts and free ligands [9]. The antibacterial activity against *Staphyloccocus aureus* and *Escherichia coli* and antifungal activity against *Aspergillus niger, Aspergillus fumigates* and *Fusarium odum* of Pd (II), Pt (II), Rh (II) and Ir (II) complexes with diacetylpyridine bis(thiosemicarbazone) was reported by Tyagi and Chandra (2012). They observed that Pd (II) complex was highly active than other metal complexes [10]. They also studied the biological activity of Cr (III) and Mn (II) complexes with macrocyclic ligand having thiosemicarbazide moiety [11].

Rai et al. (2013 & 2014) synthesized and tested antibacterial activity of cobalt (II), copper (II) and nickel (II) complexes with Schiff base 2-butyl thioquinazoline 4(3H) thiosemicarbazone against gram positive bacteria Candida albicans and gram negative bacteria Escherichia coli. They proposed from the results that all of the metal complexes exhibit more antibacterial activity than the parent ligand [12, 13].

3.2 Antifungal Activity:

Metal complexes of thiosemicarbazones also exhibit antifungal activity against pathogens [14]. Researchers generally observed that copper (II) complexes of these Schiff base ligands have shown a strong inhibition against *Candida albicans*, *Aspergillus niger* and other pathogenic fungi. The enhanced antifungal activity involves the ability of the complexes to interfere in fungal membrane integrity and metabolic processes. Nickel (II) and cobalt (II) show antifungal action against the species like *Rhizopus stolonifer* and *Aspergillus niger*.

Rodriguez-Argüelles (2009) studied antibacterial and antifungal activity of complexes of 2-acetyl-γ-butyrolactone and 2-furancarbaldehyde thiosemicarbazones. Tyagi and Chandra (2012) reported antifungal activity against *Aspergillus niger, Aspergillus fumigates* and *Fusarium odum* of Pd (II), Pt (II), Rh (II) and Ir (II) complexes with diacetylpyridine bis(thiosemicarbazone). They observed that Pd (II) complex was highly active than other metal complexes [15]. Al-Amiery et al (2012) also reported significant antifungal and antioxidant activities of pyrrolidone thiosemicarbazone complexes of copper, cobalt and nickel against selected types of fungi [16].

In another study, copper (II), nickel (II) and zinc (II) complexes of acetone thiosemicarbazone were synthesized and observed pharmacological properties by Kpomah et al. (2016). They investigate the antifungal activities of complexes against *Aspergillus niger*, *Penicillium species*, *Rhizopus* and *Candida albicans*. The research study suggested that the free ligand thiosemicarbazone showed very less antifungal activity against the fungi while zinc complexes exhibited moderate and copper and nickel showed greater antifungal activity [17].

3.3 Antiviral Activity:

The antiviral potential of some metal complexes with thiosemicarbazone Schiff bases have been reported. These complexes inhibit viral replication by interacting with the viral enzymes and exhibits activity against viruses such as human immunodeficiency virus (HIV), SARS related viruses and cowpox viruses [20]. Their ability to interact with viral proteins and nucleic acids makes them important for development of antiviral drugs. Although, further studies are required in order to understand the mechanism of antiviral activity of these metal complexes. Some copper (II) and cobalt (II) complexes exhibit inhibitory effects against herpes simplex virus (HSV) and influenza.

Giorgio Pelos (2010) studied the antiviral activity against retroviruses HIV-1 and HTLV-1/-2 of the metal complexes of thiosemicarbazone, [bis(citronellalthiosemicarbzonato) nickel(II)] and [aqua (pyridoxalthiosemicarbazonato) copper(II)] chloride monohydrate. The metal complexes show antiviral activities only against HIV. They also observed that the most anti-HIV activity was exhibited by the copper (II) complex [18]. In the year 2020, Fernandes et al. reported that cobalt (II) complexes with thiosemicarbazones exhibited antiviral potential against chikungunya virus infection. They performed molecular docking analysis of these complexes with different bacterial strains and also determined minimal inhibitory and minimal bacterial concentration values which were suggestive of high potential of these complexes against chikungunya virus by lowering the viral replication [19].

3.4 Antioxidant Activity:

Many transition metal complexes of these Schiff bases can act as antioxidants by scavenging free radicals and reducing oxidative damage. These complexes help in reducing oxidative stress which is linked to many diseases including cancer, cardiovascular diseases and neurodegenerative disorders. Recent studies have shown that thiosemicarbazone based metal complexes of copper and zinc exhibit significant antioxidant activity which may be due to their redox properties and ability to stabilize free radicals.

Yakkate et al. (2010) synthesized copper (II) and nickel (II) complexes of bis(phenylthiosemicarbazone) and reported that these complexes exhibited antioxidant and antibacterial activities. Al-Amiery et al (2012) studied a significant antioxidant activities of metal complexes of copper (II), cobalt (II) and nickel (II) with pyrrolidone thiosemicarbazone Schiff base ligand [21].

3.5 Anticancer Activity:

Cancer disease has become a serious global health problem and is a leading cause of death worldwide. Cancer involves the uncontrolled cell growth in the human body and has a potential to spread in other body parts. Generally, chemotherapy technique is used for the treatment of localized and metastasized cancer. However, the chemotherapeutic drugs exhibit very serious side effects in the human body. Therefore, the development of more effective drugs for cancer patients achieved much attention by researchers. Some metal based drugs such as cisplatin, carboplatin, oxaliplatin etc. are suggested for cancer patients. cisplatin is most acceptable anticancer drug throughout the world [22].

The Schiff base metal complexes of thiosemicarbazone studied for anticancer properties which could be used as potent drugs and diagnostic agents. Jansson et al. (2010) reported antitumor activity of copper (II) complexes of 2-acetylpyridine-4,4-dimethyl-3-thiosemicarbazone (HAp44mT) and di-2-pyridylketone-4,4-dimethyl-3-thiosemicarbazone (HDp44mT) [23]. Another report were published by Palanimuthu et al (2013) which suggested that copper complexes of glyoxal-bis(4-methyl-4-phenyl-3-thiosemicarbazone) ligand showed strong cytotoxicity against various human cancer cells. These copper complexes exhibited similar potency as that of Adriamycin, an anticancer drug. The anticancer activity of copper complexes was found to be higher than the corresponding zinc complexes [24].

Singh et al. (2020) observed anticancer potency of copper (II) complexes of thiosemicarbazone. They observed that these complexes are capable of breaking DNA strands through both oxidative and hydrolytic mechanisms. They found that these copper complexes were more efficient antitumor agent as compared to cisplatin and etoposide. In addition, these copper (II) thiosemicarbazone complexes exhibited more activity than the nickel and platinum complexes [25]. Moreover, many other researchers also examined the anticancer properties of Schiff base metal complexes of thiosemicarbazone [26-28].

IV. ADVANTAGES, CHALLENGES AND FUTURE PROSPECTS:

The metal complexes of thiosemicarbazones exhibit several advantages. These complexes have stronger biological activities than the free ligands and also have enhanced selectivity towards the biological target cells by the substitution in ligand. The increased lipophilicity of metal complexes accelerates the penetration of lipid bilayers, destabilization of membrane integrity and cause cytoplasmic leakage in microbes. These factors lead to rapid cell death in bacteria and fungi.

Despite the advantages of these complexes, there are some challenges and limitations. Some metal complexes may exhibit toxicological effects and have limited stability under physiological conditions. Furthermore, the metal complexes also show difficulty to obtain the optimal drug delivery. It has been observed that most of the related studies are limited to the laboratory research only. Therefore, it is very essential for these complexes to conduct the clinical studies.

The focus of future research in this field should be on improving more selectivity and less toxicity of the metal complexes against the disease cells and on the development of targeted drug delivery systems. The synthesis of multifunctional

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complexes having combined therapeutic effects and the application of computational tools such as molecular docking and ADME analysis can help in designing more effective metal complexes. In addition, the advancement in bioinorganic chemistry and nanotechnology may increase the potential of these metal complexes in medicinal field.

V. CONCLUSION:

Transition metal complexes containing thiosemicarbazone represent a strong innovative approach in the field of medicinal chemistry. The broad spectrum biological activities of these complexes, including antimicrobial, antiviral, anticancer and antioxidant properties, makes them ideal for drug development. Furthermore, these complexes exhibit DNA interaction, enzyme inhibition, redox modulation and cell membrane disruption which suggest about their therapeutic potential. The chelating property and involvement of metal ions in biological processes are responsible major factors for the enhanced activity of these complexes compared to free ligand.
However, further research is necessary to overcome limitations and improve therapeutic potential of complexes. These metal complexes may play an important role in the production of novel and effective drugs with the continued research and advancements.

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