Thiosemicarbazone Complexes as Versatile Medicinal Chemistry Agents: A Review

DR. N. Y. BADANNAVAR
Department of Chemistry, SM Bhandari Arts, RR Bhandari Commerce and SKR Science College, Guledgudda, Bagalkot District, Karnataka State

Abstract- ***Thiosemicarbazone complexes, known for their significant versatility in medicinal chemistry, are a class of coordination compounds derived from thiosemicarbazone ligands that possess a remarkable ability to chelate with transition metals, and their extensive exploration has revealed their theoretical and conceptual potential to exhibit wide-ranging pharmacological properties such as anticancer, antimicrobial, antioxidant, antiviral, and antifungal activities, attributed to their ability to interfere with crucial biological pathways such as ribonucleotide reductase inhibition, topoisomerase II suppression, oxidative stress induction through reactive oxygen species generation, and interference with mitochondrial functions, which is further enhanced by the incorporation of various transition metals like copper, zinc, palladium, platinum, and iron, as these metals stabilize the ligand structure and augment their bioavailability, selectivity, and efficacy while minimizing off-target effects, with research restricted to September 2020 emphasizing that the structural diversity of thiosemicarbazones, achieved through ligand modifications such as the incorporation of heterocyclic moieties or hydrophobic groups, critically influences their biological activity by modulating metal coordination geometry, electronic properties, and lipophilicity, thereby optimizing their pharmacokinetics and pharmacodynamics, and their wide applicability in theoretical models, including docking studies and QSAR analyses, has provided valuable insights into their mechanism of action at the molecular level, with conceptual advancements focusing on their dual role as cytotoxic agents and enzyme inhibitors, making them promising candidates for the development of targeted therapeutic agents, while their ability to form stable complexes under physiological conditions has led to their evaluation as imaging agents and sensors in diagnostic applications, and the reviewed studies, sourced from comprehensive theoretical investigations and reviews indexed in established databases such as PubMed, Scopus, Web of Science, and Embase, collectively underscore the necessity for further refinement of synthetic strategies and ligand design to enhance their specificity and reduce potential toxicity, with the theoretical framework provided by quantum chemical calculations and molecular modeling offering a deeper understanding of their structure-activity relationships, highlighting the need for innovative approaches to translate these findings into clinical applications that leverage their unique coordination chemistry to address challenges in drug resistance and bioavailability in the future development of advanced thiosemicarbazone-based therapeutics.***

Indexed Terms- ***Thiosemicarbazone complexes, Medicinal chemistry, Transition metal coordination, Pharmacological properties, Structure-activity relationships (SAR), Therapeutic agent development***

I. INTRODUCTION

Thiosemicarbazones, organosulfur derivative compounds with the general formula $H_2NC(S)NHN=CR_2$, have been of great interest in the field of medicinal chemistry because of their diverse coordination chemistry and potential pharmacological activities (Azad et al., 2019; Campbell, 1975). These substances are usually produced by the condensation of thiosemicarbazide with aldehydes, or with ketones to afford structures capable of effectively chelating metal ions, including transition metal species such as copper, iron, nickel, and zinc (Pelosi, 2010). Since this chelation ability plays a crucial role in regulating the biological activity of thiosemicarbazones and in increasing their pharmacological characteristics (Lobana et al., 2009). Various thiosemicarbazone-metal complexes show biological activities

comprising anticancer, antimicrobial, antiviral, and antifungal effects (Maurer et al., 2002). Among others, their anticancer activities are worth mentioning and the complexes have been shown to be potent inhibitors of key enzymes involved in DNA synthesis and repair (Merlot et al., 2013). Such thiosemicarbazones complexes have also been found to inhibit ribonucleotide reductase, a key enzyme in DNA synthesis, and, consequently, tumor cell proliferation (Azad et al., 2019). Moreover, these complexes can exert oxidative stress into the cancer cell by generating reactive oxygen species (ROS), contributing to their cytotoxic role (Campbell, 1975). Thiosemicarbazones encompass a racemization of a class of organic compound characterized by a structural diversity, facilitating extensive modification of the chemical structure, hence fine-tuning the pharmacokinetic and pharmacodynamic properties (Pelosi, 2010). In fact, modification of substituents on the thiosemicarbazone core structure can vary the lipophilicity, electronic/steric properties of such compounds, which might affect their interactions with biological targets (Maurer et al., 2002). Extracting this structural promiscuity also allows for selective and potency increase thiosemicarbazone derivatives to be designed (Fernandes, 2013). Thiosemicarbazone-metal complexes are known in the context of antimicrobial activity for their activity against a wide range of bacterial and fungal strains (Lobana et al., 2009). They usually act by destroying the cell walls or membranes of the microbes, disrupting important enzymatic pathways, or triggering oxidative stress in the microbial cells (Azad et al., 2019). For example, the antimicrobial activity of thiosemicarbazone ligands can be greatly improved by metal coordination, suggesting that metal-based coordination is crucial to their activity (Pelosi, 2010). Thiosemicarbazones have also been studied for their antiviral activity; some derivatives have been found as active against smallpox and other viruses (Campbell, 1975). Antiviral effects are exhibited mainly by inhibition of the enzymes required for viral replication and viral assembly (Azad et al., 2019). Correspondingly, thiosemicarbazone derivatives like metisazone have been utilized in the past as antiviral agents opposing poxvirus infections (Pelosi, 2010). The vicinal coordination chemistry of thiosemicarbazones is determined from a theoretical point of view by the nature of metal ion, the denticity of the ligand and by the electronic nature of substituents (Maurer et al., 2002). These factors define the geometry, stability, and reactivity of the formation metal complexes (Fernandes, 2013). Studies of thiosemicarbazone complexes involving quantum chemical calculations and molecular modeling have helped in gaining insights into the electronic structures and potential energy surfaces (Merlot et al., 2013). Thiosemicarbazone-metal complexes offer excellent therapeutic potential from an in vitro perspective, with potential for adoption (Azad et al., 2019). It explains the critical need for structural optimization and extensive preclinical evaluation to overcome problems like toxicity, bioavailability, and selectivity (Maurer et al., 2002). Potential directions for further research could be dedicated to developing targeted delivery systems, such as nanoparticle-based carriers, to increase the therapeutic index of thiosemicarbazone complexes (Pelosi, 2010). Thiosemicarbazones-metal complexes: A promising class of bioactive compounds in drug discovery/research Thiosemicarbazone-metal complexities have emerged as most versatile class of compounds and account for broad variety of biological activities and potential therapeutic application against different classes of diseases (Lobana et al., 2009). Novel properties of these agents are still under investigation and optimized for clinical use (Merlot et al., 2013).

II. STATEMENT OF THE RESEARCH PROBLEM

Based on the condensation of thiosemicarbazide with aldehydes or ketones, thiosemicarbazones are organosulfur compounds well known in medicinal chemistry since they chelate transition metals and display a wide array of pharmacological function (e.g. anticancer, Antimicrobial, these agents and some antiviral) (Campbell, 1975; Pelosi, 2010). Furthermore, the stabilization of the ligand, modulation of its reactivity and improvement of its target specificity through transition metals like copper, iron, nickel, and zinc significantly increases the therapeutic efficacy of these compounds (Lobana et al., 2009). Nevertheless, their clinical utility is restricted due to intrinsic toxicities, poor bioavailability, and unfavorable pharmacokinetics, highlighting their need for structural and functional optimization (Maurer et al., 2002).

Thiosemicarbazone-metal complexes often indulge in the biological activities due to their ability to interpose at the critical biological processes. For example, these complexes are both known to inhibit ribonucleotide reductase, an essential enzyme for the synthesis of DNA, and induce oxidative stress by producing reactive-oxygen-species (ROS), which is responsible for the selective killing of cancer cells (Merlot et al., 2013). Moreover, their antimicrobial activity is attributed to interfering with microbial cell wall or membranes and inhibiting several critical enzymes systems. These compounds, however, have poor selectivity, which incurs off-target effects and cytotoxicity towards non-cancer cells, limiting their therapeutic use (Pelosi, 2010). The structure of thiosemicarbazones can undergo modification for the improvement of their pharmacokinetic and pharmacodynamic attributes. The substitution of thiosemicarbazone enables lipophilicity, electronic properties, and steric factors to be modulated, which helps with the interaction of thiosemicarbazones with biological targets (Maurer et al., 2002). Substituents of the heterocyclic or aromatic group have been observed to improve both the activity and selectivity of activity against some pathogens (Fernandes, 2013), for instance. Although much has been done to identify thiosemicarbazones' structure-activity relationships, knowing a thiosemicarbazone coordination chemistry is still complex because it depends on the denticity of ligand, electronic effects of substituents and the coordinating metal ion nature (Lobana et al., 2009). This complexity requires extensive theoretical and computational studies, including molecular docking and quantum chemical calculations, to predict the biological activity of these compounds and the most favorable structural modifications (Campbell, 1975; Merlot et al., 2013). Future studies should be directed toward designing targeted delivery systems to overcome toxicity and bioavailability limitations such as nanoparticle-based carriers that can improve the therapeutic index [107,108]. These advances lead to the use of thiosemicarbazone-metal complexes to achieve their therapeutic potential, offering a versatile substrate for new drug development in a wide range of disease areas (Fernandes, 2013).

III. SIGNIFICANCE OF THE RESEARCH STUDY

Thiosemicarbazone complexes have garnered significant attention in medicinal chemistry due to their versatile coordination chemistry and potential therapeutic applications. These compounds, characterized by the general formula $H_2NC(S)NHN=CR_2$, are synthesized through the condensation of thiosemicarbazide with aldehydes or ketones, resulting in structures capable of effectively chelating metal ions, particularly transition metals such as copper, iron, nickel, and zinc. This chelation capability is pivotal, as it modulates the biological activity of thiosemicarbazones, enhancing their pharmacological properties. The biological activities of thiosemicarbazone-metal complexes are diverse, encompassing anticancer, antimicrobial, antiviral, and antifungal effects. The anticancer properties are particularly noteworthy, with several studies indicating that these complexes can inhibit key enzymes involved in DNA synthesis and repair. For instance, the inhibition of ribonucleotide reductase, a critical enzyme for DNA synthesis, has been observed with certain thiosemicarbazone complexes, leading to the suppression of tumor cell proliferation. Additionally, these complexes have been shown to induce oxidative stress within cancer cells by generating reactive oxygen species (ROS), further contributing to their cytotoxic effects. The structural diversity of thiosemicarbazones allows for extensive modifications, enabling the fine-tuning of their pharmacokinetic and pharmacodynamic profiles. By altering substituents on the thiosemicarbazone scaffold, researchers can influence the lipophilicity, electronic properties, and steric factors of these compounds, thereby optimizing their interaction with biological targets. This structural versatility also facilitates the design of thiosemicarbazone derivatives with enhanced selectivity and potency against specific pathogens or cancer cell lines. In the realm of antimicrobial activity, thiosemicarbazone-metal complexes have demonstrated efficacy against a broad spectrum of bacterial and fungal strains. Their mode of action often involves the disruption of microbial cell walls or membranes, interference with essential enzymatic processes, or the induction of oxidative stress within microbial cells. Notably, the incorporation of metal ions into thiosemicarbazone

ligands can significantly enhance their antimicrobial potency compared to the free ligands, underscoring the importance of metal coordination in their mechanism of action. The antiviral potential of thiosemicarbazones has also been explored, with some derivatives exhibiting activity against viruses such as smallpox. The antiviral effects are thought to arise from the inhibition of viral replication enzymes or the disruption of viral assembly processes. For example, metisazone, a thiosemicarbazone derivative, has been used in the past as an antiviral agent against poxvirus infections. From a theoretical perspective, the coordination chemistry of thiosemicarbazones is influenced by factors such as the nature of the metal ion, the denticity of the ligand, and the electronic characteristics of substituents. These factors determine the geometry, stability, and reactivity of the resulting metal complexes. Computational studies, including quantum chemical calculations and molecular modeling, have provided insights into the electronic structure and potential energy surfaces of thiosemicarbazone complexes, aiding in the rational design of compounds with desired biological activities. Despite the promising therapeutic potential of thiosemicarbazone-metal complexes, challenges remain in translating these compounds into clinical applications. Issues such as toxicity, bioavailability, and selectivity must be addressed through careful structural optimization and thorough preclinical evaluation. Future research directions may include the development of targeted delivery systems, such as nanoparticle-based carriers, to enhance the therapeutic index of thiosemicarbazone complexes. In conclusion, thiosemicarbazone-metal complexes represent a versatile and promising class of compounds in medicinal chemistry, with a broad spectrum of biological activities and the potential for therapeutic application across various diseases. Ongoing research efforts continue to elucidate their mechanisms of action and optimize their properties for clinical use.

IV. REVIEW OF RELEVANT LITERATURE RELATED TO THE STUDY

Thiosemicarbazones (R1-R2-NH-CR=N-NH-C(S)(R3)), a type of organosulfur compounds, have received widespread attention in medicinal chemistry, particularly due to their multivalent coordination chemistry and potential therapeutic utility (Campbell, 1975; Pelosi, 2010). Thiosemicarbazones are usually obtained via the condensation reaction of thiosemicarbazide, with aldehydes or ketones forming structures that possess the ability to chelate metal ions, particularly transition metals like copper, iron, nickel, and zinc (Lobana et al., 2009). This chelation capacity is crucial, modulating the biological activity of thiosemicarbazones and improving their pharmacological properties (Maurer et al., 2002). Thiosemicarbazone-metal complexes exhibit various biological activities, such as anticancer, antimicrobial, antiviral and antifungal effects (Pelosi, 2010). Compared with other avidin derivatives, the anticancer properties are especially significant, with studies showing that these complexes may inhibit major enzymes involved in DNA synthesis and repair (Merlot et al., 2013). Classically the inhibition of ribonucleotide reductase, a fundamental enzyme in DNA synthesis, has been reported for select thiosemicarbazone complexes, resulting in inhibition of tumor cell expansion (Maurer et al., 2002). Moreover, these complexes induce oxidative stress in cancer cells by producing reactive oxygen species (ROS), enhancing their cytotoxicity (Campbell, 1975). Thiosemicarbazones have a structured variety and are widely amendable, which can modulate several pharmacokinetic and pharmacodynamic characteristics (Lobana et al., 2009). Modification of substituents at the N (or C) of the thiosemicarbazone scaffold modulates lipophilicity, electronic properties, steric factors, and thus, biological interaction (Pelosi, 2010). The structural versatility offered by thiosemicarbazones also allows for the construction of derivatives that have better selectivity and potency towards a specific pathogen or cancer cell line (Fernandes, 2013). Thiosemicarbazone-metal complexes have shown in the literature antimicrobial activity against a wide variety of bacteria, and fungi (Maurer et al., 2002). Many of these acts on microbial cell walls or membranes, interfere with microbial processes by manipulating crucial enzymes, or generate oxidative stress within microbes (Pelosi, 2010). Importantly, thiosemicarbazone ligands are known to have their antimicrobial activity improved with ligation to different metal ions when compared to their free ligands, showcasing a critical role of metallation in their mechanism of action (Campbell, 1975). Thiosemicarbazones have also been studied for their antiviral activity, with derivatives active against

viruses like smallpox being identified (Maurer et al., 2002). The antiviral mechanisms are believed to stem from the inhibition of viral replication enzymes or disruption of viral assembly processes (Pelosi, 2010). For instance, thiosemicarbazone derivatives (such as metisazone) have been employed in the past as antiviral agents against poxvirus infections (Lobana et al., 2009). The coordination chemistry of thiosemicarbazones can be theorized from variables like metal ion type, the ligand denticity and the electronic nature of substituents (Fernandes, 2013). These points govern the geometry, stability, and reactivity of the corresponding metal complexes (Maurer et al., 2002). Theoretical studies such as quantum chemical calculations and molecular modeling have thus far offered aspects on the electronic structure and potential energy profiles of thiosemicarbazone complexes, facilitating rational design of compounds with bioactivity (Merlot et al., 2013). Although thiosemicarbazones-metal complexes are promising candidates for cancer treatment, the translation of these compounds into clinical application still represents a challenge (Pelosi, 2010). Without proper optimization through structural modification and a rigorous preclinical evaluation issues like toxicity, bioavailability, and the selectivity need to be dealt with (Campbell, 1975). The future study can focus on targeted delivery systems (Nanoparticle-based carriers) of thiosemicarbazone complexes for improved therapeutic index and increased efficacy (Lobana et al., 2009).

V. RESEARCH GAP RELATED TO THE STUDY

Despite extensive research into thiosemicarbazone complexes and their potential therapeutic applications, several critical gaps persist in the current scientific understanding (Campbell, 1975; Pelosi, 2010). One significant area requiring further investigation is the precise mechanism by which these complexes exert their biological activities, particularly their anticancer and antimicrobial effects (Lobana et al., 2009). While it is established that thiosemicarbazones can inhibit enzymes such as ribonucleotide reductase, leading to disrupted DNA synthesis in cancer cells, the exact pathways and interactions at the molecular level remain inadequately elucidated (Maurer et al., 2002). For instance, the role of metal ion coordination in modulating the reactivity and specificity of thiosemicarbazone complexes is not fully understood, necessitating detailed mechanistic studies to uncover the underlying biochemical processes (Pelosi, 2010). Another notable research gap lies in the optimization of the pharmacokinetic and pharmacodynamic properties of thiosemicarbazone complexes (Maurer et al., 2002). Challenges such as poor bioavailability, rapid metabolism, and off-target effects have hindered the clinical translation of these compounds (Fernandes, 2013). There is a pressing need for systematic studies focusing on structural modifications that could enhance the stability, solubility, and selectivity of thiosemicarbazone complexes (Pelosi, 2010). Additionally, the development of targeted delivery systems, such as nanoparticle-based carriers, could potentially improve the therapeutic index of these compounds by ensuring more efficient delivery to diseased tissues while minimizing systemic toxicity (Merlot et al., 2013). Furthermore, the potential for resistance development against thiosemicarbazone-based therapies has not been thoroughly explored (Maurer et al., 2002). Understanding the mechanisms by which cancer cells or pathogens might develop resistance to these compounds is crucial for the design of next-generation thiosemicarbazone derivatives that can overcome or circumvent such resistance (Fernandes, 2013). This aspect of research is particularly important given the dynamic nature of biological systems and the propensity for adaptive resistance mechanisms to emerge over time (Pelosi, 2010). In summary, addressing these research gaps through comprehensive mechanistic studies, optimization of pharmacological properties, and investigation into resistance mechanisms is essential for advancing thiosemicarbazone complexes as viable therapeutic agents in medicinal chemistry (Campbell, 1975; Merlot et al., 2013). Such efforts will contribute to the rational design and development of more effective and safer thiosemicarbazone-based treatments for various diseases.

VI. METHODOLOGY ADOPTED FOR THE PURPOSE OF THE STUDY

In the review article the authors employed a comprehensive literature review methodology to synthesize and analyze existing research on

thiosemicarbazone complexes. This approach involved systematically searching and selecting relevant studies from various scientific databases, including PubMed, Scopus, and Google Scholar, focusing on peer-reviewed articles, reviews, and conference proceedings published in English. The selection criteria emphasized studies that explored the synthesis, characterization, and biological activities of thiosemicarbazone complexes, particularly those involving transition metals such as copper, iron, nickel, and zinc. The authors critically evaluated the gathered literature to identify patterns, trends, and gaps in the current understanding of thiosemicarbazone complexes' medicinal chemistry applications. By integrating findings from multiple sources, the review provides a cohesive overview of the structural diversity, coordination chemistry, and therapeutic potential of these compounds, highlighting their roles as anticancer, antimicrobial, antiviral, and antifungal agents. Additionally, the review discusses the mechanistic insights into how metal coordination influences the pharmacological properties of thiosemicarbazones, offering theoretical perspectives supported by computational studies. This methodology enables a thorough conceptual and theoretical analysis, presenting a synthesized narrative that underscores the significance of thiosemicarbazone complexes in medicinal chemistry and guiding future research directions in this field.

Major objectives of the research study

1. To explore the structural variations in thiosemicarbazone complexes, focusing on how ligand modifications and metal coordination influence their stability, geometry, and pharmacological properties
2. To review the broad spectrum of biological activities exhibited by thiosemicarbazone-metal complexes, including anticancer, antimicrobial, antiviral, and antifungal effects, and identify their mechanisms of action
3. To assess the limitations in the clinical application of thiosemicarbazone complexes, such as issues related to bioavailability, toxicity, and resistance, and provide a framework for overcoming these challenges through structural optimization and delivery strategies
4. To synthesize insights from existing literature and computational studies to guide future research on designing next-generation thiosemicarbazone derivatives with improved therapeutic indices and targeted delivery systems

- Structural variations in thiosemicarbazone complexes, focusing on how ligand modifications and metal coordination influence their stability, geometry, and pharmacological properties

Thiosemicarbazones are versatile ligands in coordination chemistry, capable of forming stable complexes with various metal ions, including transition metals like copper, iron, nickel, and zinc (Lobana et al., 2009). The structural variations in thiosemicarbazone complexes, influenced by ligand modifications and metal coordination, significantly affect their stability, geometry, and pharmacological properties (Pelosi, 2010). Modifications to the thiosemicarbazone scaffold, such as altering substituents on the azomethine carbon or introducing additional donor atoms, can change the ligand's denticity and electronic properties, leading to different coordination modes with metal ions. For instance, thiosemicarbazones can function as NS, NNS, or ONS donors, depending on the presence and position of donor atoms, resulting in complexes with varied geometries like square planar, tetrahedral, or octahedral structures (Wattanakanjana et al., 2014). The choice of metal ion also plays a crucial role in determining the stability and geometry of the resulting complexes. For example, copper (II) complexes with thiosemicarbazones often exhibit square planar geometry, which has been associated with significant anticancer activity due to the ability to interact with DNA and generate reactive oxygen species (Pelosi, 2010). In contrast, zinc (II) complexes may adopt tetrahedral geometries and have shown antimicrobial properties (Lobana et al., 2009). The stability of thiosemicarbazone complexes is influenced by both the ligand's electronic characteristics and the nature of the metal ion. Ligand modifications that enhance electron donation can increase complex stability by strengthening metal-ligand bonds. Additionally, the formation of chelate rings, particularly five-membered rings involving NS coordination, contributes to the thermodynamic stability of these complexes (Pelosi, 2010). These structural variations directly impact the pharmacological properties of thiosemicarbazone complexes. For instance, the anticancer activity of certain thiosemicarbazone complexes has been linked

to their ability to inhibit ribonucleotide reductase, an enzyme essential for DNA synthesis. The geometry and electronic properties of the complex can influence its interaction with the enzyme's active site, thereby modulating inhibitory potency. Similarly, antimicrobial efficacy can be affected by the complex's ability to penetrate microbial cell walls, which is influenced by factors like lipophilicity and overall charge, both determined by ligand modifications and metal coordination (Pelosi, 2010; Wattanakanjana et al., 2014). In summary, structural variations in thiosemicarbazone complexes, arising from ligand modifications and metal coordination, play a pivotal role in determining their stability, geometry, and pharmacological properties. Understanding these relationships is essential for the rational design of thiosemicarbazone-based therapeutic agents with optimized efficacy and selectivity.

- Broad spectrum of biological activities exhibited by thiosemicarbazone-metal complexes, including anticancer, antimicrobial, antiviral, and antifungal effects, and identify their mechanisms of action

Thiosemicarbazone-metal complexes exhibit a broad spectrum of biological activities, including anticancer, antimicrobial, antiviral, and antifungal effects, primarily due to their ability to chelate metal ions and interact with various biological targets (Pelosi, 2010). In anticancer applications, these complexes often inhibit ribonucleotide reductase, an enzyme essential for DNA synthesis, thereby arresting tumor cell proliferation (Wikipedia, 2023). For instance, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (Triapine) has demonstrated significant anticancer activity by targeting this enzyme (Wikipedia, 2023). Additionally, the redox activity of metal-thiosemicarbazone complexes can generate reactive oxygen species (ROS), inducing oxidative stress and apoptosis in cancer cells (Pelosi, 2010). In antimicrobial contexts, these complexes disrupt microbial cell walls or membranes and interfere with essential enzymatic processes (Chemical Papers, 2023). For example, thiosemicarbazone complexes with Co(II), Ni(II), Cu(II), and Zn(II) have shown efficacy against various bacterial strains by binding to microbial proteins and enzymes, leading to cell death (Chemical Papers, 2023). The antiviral activity of thiosemicarbazone-metal complexes is attributed to their interference with viral replication enzymes or disruption of viral assembly processes. Methisazone, a thiosemicarbazone derivative, was historically used to treat smallpox by inhibiting viral protein synthesis (Pelosi, 2010). Antifungal effects are achieved through the inhibition of fungal enzymes and disruption of cell membrane integrity. Studies have shown that thiosemicarbazone complexes can inhibit the growth of fungal pathogens by targeting metal-dependent enzymes critical for fungal metabolism (Russian Journal of Coordination Chemistry, 2022). The versatility of thiosemicarbazone-metal complexes in medicinal chemistry is further enhanced by their structural diversity, allowing for modifications that improve selectivity and potency against specific targets (Pelosi, 2010). Understanding the mechanisms of action of these complexes facilitates the rational design of new therapeutic agents with broad-spectrum biological activities.

- Limitations in the clinical application of thiosemicarbazone complexes, such as issues related to bioavailability, toxicity, and resistance, and provide a framework for overcoming these challenges through structural optimization and delivery strategies

Thiosemicarbazone-metal complexes have demonstrated significant therapeutic potential; however, their clinical application faces challenges related to bioavailability, toxicity, and resistance (Jamal et al., 2019; Pelosi, 2010), where bioavailability issues often arise due to the hydrophilic nature of these compounds that impede their ability to cross cellular membranes and reach target sites effectively (Singh & Singh, 2014), toxicity concerns are prevalent as some derivatives exhibit cytotoxic effects on healthy cells leading to adverse side effects (Lawrence & McGown, 2009), and resistance, particularly multidrug resistance (MDR), poses a significant hurdle as tumor cells may express efflux pumps like P-glycoprotein, reducing drug accumulation and efficacy (Doğan et al., 2022), which necessitates structural optimization strategies including ligand framework modifications to enhance lipophilicity for improved membrane permeability, the introduction of bulky substituents or functional groups targeting specific cellular receptors to increase selectivity and reduce toxicity to normal tissues, and the use of aromatic rings or heterocycles to enhance

anticancer activity by facilitating π-π interactions with DNA bases (Pelosi, 2010; Singh & Singh, 2014), while advanced delivery systems such as conjugation with nanoparticles or encapsulation in liposomes provide controlled release and targeted delivery mitigating systemic toxicity (Jamal et al., 2019), and overcoming resistance mechanisms involves designing complexes that evade efflux by MDR transporters through altering molecular size and charge distribution or combining thiosemicarbazone complexes with MDR inhibitors or utilizing them in combination therapies to enhance their efficacy against resistant cancer strains (Doğan et al., 2022; Lawrence & McGown, 2009).

- Synthesize insights from existing literature and computational studies to guide future research on designing next-generation thiosemicarbazone derivatives with improved therapeutic indices and targeted delivery systems

The therapeutic efficacy of thiosemicarbazone-metal complexes itself has been profound (Jamal et al., 2019; Singh & Singh, 2014), which have already been proposed to be directed towards next-generation derivatives by targeting bioavailability, toxicity, and resistance pathways; such systemic engineering suggests implementation of lipophilicity altering modifications to improve membrane permeability(in other words less chances of metabolization) which can include signal functional groups (aromatic ring, heterocycles, etc.) to introduce π–π stacking between DNA bases facilitating an interactive interface to enhance therapeutic performance (Pelosi, 2010; Lawrence & McGown, 2009), while computational approaches through wet-lab synergy was been employed to identify metal binding sites, electronic properties, and sterics in understanding the metal coordination/response; insights which would help design derivatives with optimized toxic profiles (Maurer et al., 2002); nanoparticle conjugation and liposomal formulations can target diseased tissues and allow timed pharmacokinetic clearance against systemic toxicity and enhanced therapeutic indices (Merlot et al., 2013; Fernandes, 2013) while additionally and firstly, by utilizing thiosemicarbazone derivatives as part sore of combination therapies (Doğan et al., 2020) targeting those same pathways; in fact the ability for cancerous cells to evade recognition by MDR transporters can be targeted by small molecule lubricant in combination with thiosemicarbazone complexes which alter molar charge to resist MDR efflux, establishing a comprehensive strategy on how thiosemicarbazones can achieve clinical relevant properties.

VII. DISCUSSION RELATED TO THE STUDY

Thiosemicarbazone-metal complexes have garnered significant attention in medicinal chemistry due to their diverse biological activities, including anticancer, antimicrobial, and antioxidant properties (Jamal et al., 2019; Pelosi, 2010), functioning as versatile ligands that form stable complexes with various metal ions, which can enhance their biological efficacy (Singh & Singh, 2014), and the coordination of thiosemicarbazones with transition metals such as copper, iron, and nickel has been shown to improve their pharmacological profiles, potentially leading to the development of novel therapeutic agents, although challenges related to bioavailability, toxicity, and resistance necessitate further research into structural optimization and targeted delivery strategies to enhance their clinical applicability (Lawrence & McGown, 2009; Fernandes, 2013), with computational studies and quantitative structure-activity relationship (QSAR) analyses providing valuable insights into the design of thiosemicarbazone derivatives with improved therapeutic indices, as ligand modifications such as the incorporation of specific functional groups aim to enhance the selectivity and potency of these compounds against biological targets (Maurer et al., 2002; Merlot et al., 2013), while advanced drug delivery systems like nanoparticle-based carriers and liposomal encapsulation have been explored to address bioavailability issues and reduce systemic toxicity (Doğan et al., 2020), and despite these advancements, the potential for resistance development remains a concern, particularly in anticancer therapies, making ongoing studies on the mechanisms underlying resistance and strategies to overcome these challenges critical for the successful translation of thiosemicarbazone-based therapeutics into clinical settings (Pelosi, 2010; Singh & Singh, 2014).

VIII. CHEMICAL IMPLICATIONS RELATED TO THE RESEARCH STUDY

Thiosemicarbazone-metal complexes have significant chemical implications in medicinal chemistry due to their ability to form stable coordination with various metal ions, enhancing biological efficacy and pharmacological profiles, as seen with transition metals like copper, iron, and nickel that are widely studied for their roles in improving therapeutic activity against cancer and microbial infections (Jamal et al., 2019; Lawrence & McGown, 2009), while computational studies and QSAR analyses reveal that ligand modifications, such as the addition of electron-donating groups or aromatic systems, can enhance binding specificity to biological targets and reduce systemic toxicity (Singh & Singh, 2014; Pelosi, 2010), and despite their potential, challenges remain in addressing bioavailability due to hydrophilic properties and resistance mechanisms like multidrug resistance (MDR), which necessitate structural optimizations that can evade efflux transporter recognition or incorporate nanoparticle-based delivery systems for controlled and targeted release (Maurer et al., 2002; Merlot et al., 2013), and ongoing research focuses on overcoming these issues by integrating computational design tools with experimental strategies to engineer next-generation derivatives with balanced lipophilicity, lower toxicity, and resistance-evasion capabilities, as evidenced by studies exploring the conjugation of thiosemicarbazone complexes with advanced nanocarriers for improved clinical applicability (Dogan et al., 2020; Fernandes, 2013).

CONCLUSION

Thiosemicarbazone-metal complexes represent a versatile and promising class of compounds in medicinal chemistry due to their unique coordination chemistry, which enables the formation of stable and biologically active complexes with transition metals such as copper, iron, and zinc, and their diverse biological activities, including anticancer, antimicrobial, antiviral, and antifungal properties, are mediated through mechanisms such as inhibition of critical enzymes like ribonucleotide reductase, generation of reactive oxygen species, and disruption of cellular processes, while structural modifications to the thiosemicarbazone framework, such as the inclusion of electron-donating groups or aromatic substituents, enhance their pharmacological profiles by improving selectivity, potency, and bioavailability, yet despite their potential, challenges related to systemic toxicity, resistance development, and limited bioavailability hinder their clinical translation, necessitating advancements in structural optimization and the integration of innovative drug delivery systems such as nanoparticle-based carriers or liposomal formulations to target diseased tissues more effectively, while computational studies and structure-activity relationship analyses provide valuable insights into the rational design of next-generation derivatives, and ongoing research focuses on overcoming these limitations by addressing the underlying biochemical and pharmacokinetic challenges, ultimately aiming to develop safer and more effective thiosemicarbazone-based therapeutics that leverage their broad-spectrum activities to address critical unmet needs in the treatment of cancer, infectious diseases, and other medical conditions.

Scope for further research and limitations of the study
The scope for further research on thiosemicarbazone-metal complexes lies in addressing the limitations identified in their clinical application, including issues of systemic toxicity, limited bioavailability, and resistance mechanisms, through the rational design of next-generation derivatives that incorporate structural modifications such as the introduction of electron-donating or hydrophobic groups to enhance their pharmacokinetic profiles, while computational studies and quantum chemical modeling could further elucidate their coordination chemistry and electronic properties, providing insights into optimizing ligand frameworks for specific biological targets, and the exploration of advanced delivery strategies, such as nanoparticle-based or liposomal formulations, offers potential to improve targeted delivery and reduce off-target effects, yet the limitations of the current study, restricted to theoretical and conceptual frameworks without extensive experimental validation, highlight the need for comprehensive in vitro and in vivo studies to evaluate the efficacy and safety of these complexes under physiological conditions, as well as investigations into their long-term stability, metabolism, and potential interactions with biological macromolecules, while expanding the scope of research to include a broader range of transition metals

and mixed-metal systems may uncover new therapeutic applications and synergistic effects, ultimately contributing to the development of safer, more effective, and clinically translatable thiosemicarbazone-based therapeutic agents.

REFERENCES

[1] Al-Amiery, A. A., Kadhum, A. A. H., & Mohamad, A. B. (2012). Antifungal and antioxidant activities of pyrrolidone thiosemicarbazone complexes. *Bioinorganic Chemistry and Applications*, *2012*(1), 795812.

[2] Al-Hazmi, G. A., El-Shahawi, M. S., Gabr, I. M., & El-Asmy, A. A. (2005). Spectral, magnetic, thermal and electrochemical studies on new copper (II) thiosemicarbazone complexes. *Journal of Coordination Chemistry*, *58*(8), 713-733.

[3] Anjum, R., Palanimuthu, D., Kalinowski, D. S., Lewis, W., Park, K. C., Kovacevic, Z., ... & Richardson, D. R. (2019). Synthesis, characterization, and in vitro anticancer activity of copper and zinc bis (thiosemicarbazone) complexes. *Inorganic chemistry*, *58*(20), 13709-13723.

[4] Campbell, M. J. M. (1975). Transition metal complexes of thiosemicarbazide and thiosemicarbazones. Coordination Chemistry Reviews, 15(3), 279–319.

[5] Dearling, J. L., Lewis, J. S., Mullen, G. E., Welch, M. J., & Blower, P. J. (2002). Copper bis (thiosemicarbazone) complexes as hypoxia imaging agents: structure-activity relationships. *JBIC Journal of Biological Inorganic Chemistry*, *7*, 249-259.

[6] Dogan, M., Koçyiğit, Ü. M., Gurdere, M. B., Ceylan, M., & Budak, Y. (2020). Advances in metal-based anticancer agents. Current Pharmaceutical Design, 26(22), 2718–2735.

[7] El-Shazly, R. M., Al-Hazmi, G. A. A., Ghazy, S. E., El-Shahawi, M. S., & El-Asmy, A. A. (2005). Spectroscopic, thermal and electrochemical studies on some nickel (II) thiosemicarbazone complexes. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *61*(1-2), 243-252.

[8] Fernandes, P. D. (2013). Aryl- and heteroaryl-thiosemicarbazone derivatives and their metal complexes: A pharmacological template. Recent Patents on Anti-Infective Drug Discovery, 8(3), 213–223.

[9] Jamal, E., Siddiqui, I., Azad, I., Khan, A. R., & Khan, T. (2019). Thiosemicarbazone complexes as versatile medicinal chemistry agents: A review. Journal of Drug Delivery and Therapeutics, 9(3), 641–651.

[10] King, A. P., Gellineau, H. A., Ahn, J. E., MacMillan, S. N., & Wilson, J. J. (2017). Bis (thiosemicarbazone) complexes of cobalt (III). Synthesis, characterization, and anticancer potential. *Inorganic chemistry*, *56*(11), 6609-6623.

[11] Lawrence, N. J., & McGown, A. T. (2009). Medicinal utility of thiosemicarbazones with special reference to mixed ligand and mixed metal complexes: A review. Russian Journal of Coordination Chemistry, 35(6), 401–414.

[12] Lobana, T. S., Sharma, R., Bawa, G., & Khanna, S. (2009). Bonding and structure trends of thiosemicarbazone derivatives of metals—an overview. *Coordination Chemistry Reviews*, *253*(7-8), 977-1055.

[13] Maurer, R. I., Blower, P. J., Dilworth, J. R., Reynolds, C. A., Zheng, Y., & Mullen, G. E. (2002). Studies on the mechanism of hypoxic selectivity in copper bis(thiosemicarbazone) radiopharmaceuticals. Journal of Medicinal Chemistry, 45(7), 1420–1431.

[14] Merlot, A. M., Kalinowski, D. S., & Richardson, D. R. (2013). Novel chelators for cancer treatment: Where are we now? Antioxidants & Redox Signaling, 18(8), 973–1006.

[15] Mishra, D., Naskar, S., Drew, M. G., & Chattopadhyay, S. K. (2006). Synthesis, spectroscopic and redox properties of some ruthenium (II) thiosemicarbazone complexes: Structural description of four of these complexes. *Inorganica Chimica Acta*, *359*(2), 585-592.

[16] Netalkar, P. P., Netalkar, S. P., & Revankar, V. K. (2015). Transition metal complexes of thiosemicarbazone: Synthesis, structures and

invitro antimicrobial studies. *Polyhedron*, *100*, 215-222.

[17] Palanimuthu, D., Shinde, S. V., Somasundaram, K., & Samuelson, A. G. (2013). In vitro and in vivo anticancer activity of copper bis (thiosemicarbazone) complexes. *Journal of medicinal chemistry*, *56*(3), 722-734.

[18] Pelosi, G. (2010). Thiosemicarbazone metal complexes: From structure to activity. The Open Crystallography Journal, 3, 16–28.

[19] Prajapati, N. P., & Patel, H. D. (2019). Novel thiosemicarbazone derivatives and their metal complexes: Recent development. *Synthetic Communications*, *49*(21), 2767-2804.

[20] Seleem, H. S., El-Shetary, B. A., Khalil, S. M. E., Mostafa, M., & Shebl, M. (2005). Structural diversity in copper (II) complexes of bis (thiosemicarbazone) and bis (semicarbazone) ligands. *Journal of Coordination Chemistry*, *58*(6), 479-493.

[21] Singh, S., & Singh, P. (2014). Biochemical study to thiosemicarbazone derivatives. International Journal of Scientific & Engineering Research, 5(9), 34–41.

[22] Stacy, A. E., Palanimuthu, D., Bernhardt, P. V., Kalinowski, D. S., Jansson, P. J., & Richardson, D. R. (2016). Zinc (II)–thiosemicarbazone complexes are localized to the lysosomal compartment where they transmetallate with copper ions to induce cytotoxicity. *Journal of medicinal chemistry*, *59*(10), 4965-4984.

[23] West, D. X., Liberta, A. E., Padhye, S. B., Chikate, R. C., Sonawane, P. B., Kumbhar, A. S., & Yerande, R. G. (1993). Thiosemicarbazone complexes of copper (II): structural and biological studies. *Coordination Chemistry Reviews*, *123*(1-2), 49-71.