Review:

Review on Anticancer Activity of Essential Metal Dithiocarbamate Complexes

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Received: March 24, 2022
Accepted: July 3, 2022

DOI: 10.22146/ijc.73738

Abstract: *The importance of essential metal ions and their metal complexes in the creation of prospective medical therapies has long been recognized. In chemistry, molecular biology, and medicinal fields; the interaction of metal complexes with DNA has been a subject of study. The dithiocarbamate essential metal complex is described extensively in the literature for its various benefits and advantages. With proper use of ligands, it is proven to increase the cytotoxic activity of metal complexes against cancer cells. Some researches have shown significant progress regarding the biological activities of the dithiocarbamate essential metal complex as antimicrobial, antioxidant, and anticancer agents. Metal complexes form complexes with dithiocarbamate ligands with unique structural variations. In this study, we presented an overview of the cytotoxic effects of some dithiocarbamate essential metal complexes on cancer cells, as well as fresh approaches to the design of essential metal-based therapeutics containing dithiocarbamate and molecular targets in cancer therapy. This review may provide an update on recent developments in the medicinal use of essential metals with dithiocarbamate ligands, carried out to identify recent relevant literature. Finally, we predict that the essential metal complexed with dithiocarbamate can be a new breakthrough in the future development of cancer drugs.*

Keywords: *cytotoxic activity; dithiocarbamate; essential metal; therapeutics; cisplatin*

■ INTRODUCTION

Researchers are currently giving their interest in the production of metal complexes for several applications, particularly in the medical field. After the surprising discovery of the coordination molecule cisplatin, metal-based medicines have become a promising study area in

medicinal chemistry [1]. The cisplatin complex is in a square planar form having two labile chloride ligands and two inert ammonia ligands bonded to a platinum(II) central atom in the cis configuration [2]. The first anticancer agent used in a clinical setting is cis-platin, which is still one of the most often prescribed medications for the treatment of cancer today [3-4]. Currently, platinum-based medicines are used to treat roughly half of all cancer patients. The challenges that cis-platinum treatments encounter, such as their lack of selectivity, unpleasant side effects, resistance, and toxicity in the body, are what motivate researchers to look for more effective and selective non-platinum therapeutics [5-6].

The development of new therapeutic medicines is crucial for the treatment of cancer [7]. One of the newest drug discovery methodologies for creating therapeutic compounds is metal complex synthesis. Metal complexes have demonstrated antibacterial, antioxidant, anticancer, and antimalarial effects. The synergistic interaction between the ligand moiety and the central metal is often credited for these biological activities [8]. Metal-based anticancer medications have made great strides toward eliminating the negative effects of traditional platinum therapy. Even at the point of clinical trials, a wide variety of metal complexes, including Cu, Ni, and Zn, have been researched through *in vitro* and *in vivo* assays [9-13].

Transition metal complexes having anticancer activity of Ni, Cu, Zn, and other metals have been shown to outperform cis-platin-based therapies. Zn is involved in about 200 enzymatic biochemical activities in the human body [14]. Ni complexes with oxoaporfin derivatives have very high cytotoxicity values against tumor cells [15]. Zn is the second-most common essential transition metal ion in the human body whereas DNA can covalently attach to Zn's radius [16-17]. Zn plays a part in the development, differentiation, and demise of cells, among other biological processes. In various *in vitro* investigations, Zn complexes have shown promise in reducing the growth of a variety of cancers without having any cytotoxic or tumor-suppressive effects on malignant cells.

Zn(II) ions are necessary for the proper folding and operation of a variety of cellular enzymes and transcription factors in a number of cellular activities. Zn(II) may function as an intracellular second messenger and trigger apoptosis as previously reported [18]. Zn is required for appropriate cell membrane construction and function. Some Zn complexes show promising results in anticancer efficacy and reduce the number of malignancies [18]. There has been an increase in Zn(II) complexes containing N- and S-donors in recent years, to develop antibacterial and anticancer medicines with improved activity, selectivity, and bioavailability, as well as lower toxicity than current therapeutic options. Matsukura and Tanaka [19] described the chemical and biological features of the Zn L-carnosine complex, as well as its benefits as a membrane-protective anti-ulcer medication with a long-term healing effect. It was revealed that Cu(II) and Zn(II) complexes were implicated in DNA strand binding interactions after engaging with pyrimidine-morpholine-based ligands. The *in vitro* anticancer research of Cu(II) and Zn(II) complexes showed considerable cytotoxic ability against cancer cell lines and little toxicity to normal cell lines [20].

Several studies have been reported regarding the use of essential metals as anticancer complexes, namely Co(II), Ni(II), Cu(II), and Zn(II) which have potential as anticancer [21]. After 72 h, the Co(II) complex demonstrated stronger anticancer activity than the equivalent ligands, particularly inhibiting cancer cell proliferation by 83.22% [22]. Emodin and Mn(II) complex can increase anticancer activity [4]. The Human Serum Albumin (HSA)-Cu(Bp44Mt) combination was then shown to suppress the development of lung cancer cells *in vivo* [23]. The iron compound known as the ferrocenium complex may prevent the development of cancer cells [24].

The usage of ligands in the right way has been found to boost the biological activity of complex molecules [25]. One important group that is getting more attention today is the dithiocarbamate complex [26]. The recent literature on the anticancer properties of the dithiocarbamate essential metal complex prompted us to conduct this literature review as a significant starting point for the development of new

anticancer drugs, particularly the dithiocarbamate complex using essential metal chemistry of pharmaceuticals.

■ DITHIOCARBAMATE

Dithiocarbamates are one of the common classes of 1,1-dithiolate monoanionic ligands. Dithiocarbamate was first reported in the 19th century [27], and these ligands continue to be relevant today. Dithiocarbamate complexes have been widely synthesized using the main metal elements and transition metal elements as the central atom dithiocarbamate is a soft donor ligand that can chelate with most of the metal ions in the periodic table, including the actinides and lanthanides [28].

A molecule called dithiocarbamate that chelates metals has many uses in medicine. Infections caused by bacteria and fungi, AIDS, and most recently, cancer, have all been treated with dithiocarbamate derivatives. Current chemotherapeutic treatments have a limited ability to eradicate malignancies because of how toxic they are. As a result, numerous researchers are now involved in the hunt for novel, tailored medications in an effort to reduce side effects while enhancing therapeutic potential [29-33].

Dithiocarbamate compounds can be used as radio-chemotherapeutic treatments to target tumors [33-37]. One of the important metal-chelating antioxidants is dithiocarbamate molecules and their derivatives [38]. It has been demonstrated that the dithiocarbamate complex can inhibit cell proliferation [39]. Dithiocarbamate complex is known for its outstanding structure, which has a wide range of biological applications [40]. Multiple reports of metal dithiocarbamate complex with mixed ligands having antifungal, antibacterial, anticancer, and apoptosis-inducing properties were confirmed in a recent literature study.

A review of the literature found that metal dithiocarbamate complex with mixed ligands has antifungal, antibacterial, anticancer, and apoptosis-inducing properties. Currently, some of the metals employed in dithiocarbamate research are offered as radiopharmaceuticals as parts of diagnostic kits for use in medicine [41-43]. Dithiocarbamate compounds feature a unique structure that includes an S group that can transfer monodentate and bidentate electrons [41]. The structural variation of the dithiocarbamate complex can enhance the biological activity of the complex by using additional donor groups, such as oxygen and nitrogen groups [42].

Previous research has revealed that the dithiocarbamate metal complex has enormous anticancer potential [39,44-49]. Table 1 provides evidence of the Zn(II) dithiocarbamate complex's cytotoxic efficacy against numerous cancer cell types. The cytotoxic effectiveness of the Mn(II) dithiocarbamate complex against numerous cancer cell types is shown in Table 2. The Cu(II) dithiocarbamate compound's cytotoxic activity is displayed in Table 3.

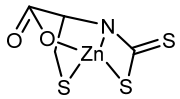
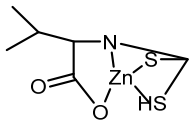
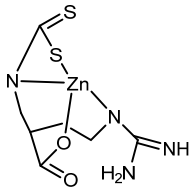
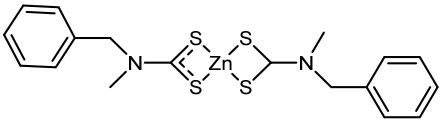
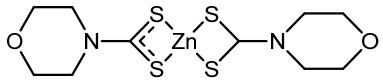
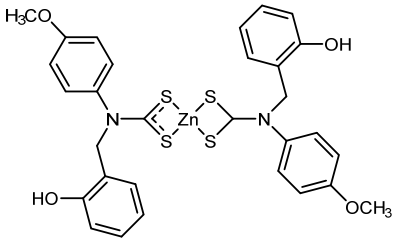
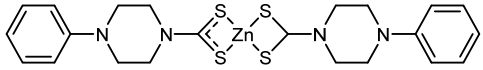
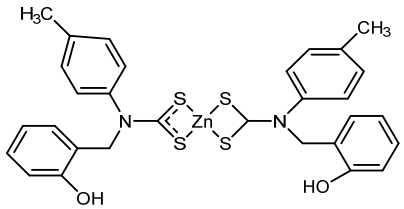
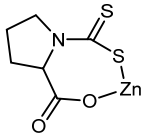
The anticancer activity of the substance was calculated using the IC_{50} value and expressed in μg/mL. Anticancer activity is defined as preventing the spread of cancer cells (antiproliferation). A chemical is more effective at slowing or halting the growth of cancer cells when its IC_{50} value is lower. On the other hand, the more the substance inhibits the proliferation of cancer cells, the higher the IC_{50} value becomes.

■ CYTOTOXIC ACTION OF Zn(II) DITHIOCARBAMATE COMPLEXES AGAINST A RANGE OF CANCER CELL LINES

The cytotoxic activity of different Zn(II) dithiocarbamate complexes against several cancer cell lines is shown in Table 1. The cytotoxicity of the Zn(II) **1** complex on MCF-7 cells was assessed using the MTS assay (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxy phenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium) was observed for 24 h. The MTS assay is one of the most commonly used assays to assess cell proliferation and cytotoxicity [56]. Because the Zn complex's IC_{50} value is lower than that of cisplatin, it has higher cytotoxicity than cisplatin in inducing morphology in MCF-7 cancer cells [17].

The Zn(II) **2** complex induces morphological changes in cancer cells by causing apoptosis and the IC_{50} value = 210.27 μg/mL, with DNA as the target cell [50]. T47D cancer cells had an IC_{50} of 3.16 μg/mL for the Zn(II) **3** complex, while fibroblast cells had an IC_{50} of 8709.63 μg/mL. These results demonstrate a considerable

Table 1. Cytotoxic action of Zn(II) dithiocarbamate complexes against a range of cancer cell lines (2018-2021)

Zn(II) dithiocarbamate complexes	Cancer cell line type	IC_{50} µg/mL	Main mechanism	Ref.
Zn(II)Cysteindithiocarbamate 	Breast MCF-7	98.60	Inhibits cell mutation process by binding to guanine from MCF-7 cancer cell DNA	[17]
Zn(II)Valinedithiocarbamate 	Breast MCF-7	210.27	Induces morphological changes in cancer cells and causes apoptosis	[50]
Zn(II)Argininedithiocarbamate 	Breast T47D	3.16	Inhibits the process of cell mutation by binding to guanine from T47D cancer cell DNA, as well as the intercalation of the ligand into the DNA gap	[51]
Zn(II) bis-(*N*-methyl-1-phenyl dithiocarbamate) 	Renal TK-10 Melanoma UACC-62 Breast MCF-7	14.28 22.74 20.10	Induces apoptosis	[47]
Zn(II)morpholinyldithiocarbamate 	Renal TK-10 Melanoma UACC-62 Breast MCF-7	8.70 16.54 3.17	Binds to DNA	[48]
Zn(II) methoxyphenyldithiocarbamate 	Lung MRC5-SV2	15.1	Induces apoptosis, DNA targets	[49]
Zn(II)bis(1-phenylpiperazinedithiocarbamato) 	Renal TK-10 Melanoma UACC-62 Breast MCF-7	13.40 15.14 8.42	DNA targets	[52]
Zn(II) 2-((*p*-tolylamino)methyl)phenolyl dithiocarbamate 	HeLa MRC5-SV2 MRC5	28.1 19.8 22.3	DNA targets	[53]
Zn(II)Prolinedithiocarbamate 	Breast MCF-7	360.10	DNA targets	[54]

cytotoxic effect of the complex chemical Zn(II) arginine dithiocarbamate on T47D cancer cells but a negligible cytotoxic effect on fibroblast cells (healthy cells). Additionally, it is possible to demonstrate that the Zn(II) arginine dithiocarbamate complex has a lower IC_{50} value than cisplatin, proving that the latter compound is less hazardous [51].

The Zn(II) bis-(*N*-methyl-1-phenyl dithiocarbamate) **4** complex was more active than the Cu and Pt complexes against the TK-10, UACC-62, and MCF-7 cell lines, with IC_{50} values of 14.28, 22.74, and 20.10 μg/mL, respectively [47]. The Sulforhodamine B (SRB) assay was used to assess the Zn(II) **5** complex against TK-10, UACC-62, and MCF-7 cancer cells. The most effective drug was morphinylditiocarbamate, which had an IC_{50} of 1.51 μg/mL against TK-10 and 2.65 μg/mL against MCF-7. With an IC_{50} of 3.17 μg/mL, the [Zn(-MphDTC)2(MphDTC)2] molecule was marginally more potent against MCF-7 cell lines than parthenolide. The Zn(II) molecule showed efficacy against TK-10 and UACC-62 at 8.70 and 16.54 μg/mL, respectively [48].

Cisplatin is more toxic to cancer cells than Zn(II) **6** complex, but it is extremely toxic to normal cells (fibroblasts). Although the cytotoxicity of Co(II) and Zn(II) complexes against cancer cells did not differ significantly, Co(II) methoxyphenyl dithiocarbamate was more cytotoxic than Zn(II) methoxyphenyl dithiocarbamate against normal cells [49]. At IC_{50} concentrations of 8.42, 13.40, and 15.14 μg/mL, the anticancer activity of Zn(II) **7** complex followed the order MCF-7, TK-10, UACC-62. The platinum complex, on the other hand, was active at a higher IC_{50} concentration of 100 μg/mL. The Zn(II) bis(1-phenylpiperazine dithiocarbamate) complex has been shown to inhibit growth because Zn is an essential element with excellent biological activity [52]. Zn is also involved in cell proliferation, differentiation, and apoptosis, among other cellular processes.

In various *in vitro* investigations, Zn complexes showed promise in reducing the growth of a variety of cancers without having any cytotoxic or tumor-suppressive effects on malignant cells. For the appropriate folding and activation of numerous cellular enzymes and transcription factors in a range of cellular functions, Zn(II) ions are necessary. According to the theory, excessive levels of Zn(II) can act as an intracellular second messenger and induce apoptosis [18-19].

In addition to conventional therapies, cisplatin, MRC5-SV2 (lung cancer cell line), and MRC5 (normal (healthy) lung fibroblast cell line) were employed. Cisplatin (6.25–100 μg/mL) significantly reduced the viability of HeLa, MRC5-SV2, and MRC-5 cells after 48 h of treatment, with IC_{50} values of 11.1, 8.6, and 15.0 μg/mL, respectively. The degree of morphological damage caused by cisplatin or the Zn(II) 2-((*p*-tolylamino) methyl)phenolyl dithiocarbamate complex correlates with viability loss. The toxicity phenotype of cisplatin and the complex was also demonstrated to be concentration dependent morphologically, with the toxicity phenotype gradually worsening with increasing concentration. These cultures exhibited tissue processes and appeared confluent, in contrast to negative control cultures that remained affixed to the substrate. Cell rounding, shrinkage, and, in some circumstances, significant cell loss are characteristics of the toxicity phenotype, which is consistent with the morphology of the many cell types investigated. HeLa cells were less sensitive to cisplatin than MRC5-SV2 cells, which were more susceptible.

HeLa cells were more susceptible to Zn(II) complexes than MRC5-SV2 and MRC5. Additionally determined were the cisplatin values and the complex selectivity index (SI). SI stands for the ratio of a substance's IC_{50} toxicity to a cancer cell line or a cancer variant of a normal cell line to a normal cell line (in this example, MRC5) (in this case, MRC5-SV2) [51]. SI > 1 indicates a more selective molecule (desirable) for cancer cells, whereas SI 1 indicates a substance that is more damaging to normal cells than cancer cells (undesired).

The cancer cell line MRC5-SV2 is approximately twice as toxic to cisplatin as normal cells, according to its SI of 1.7 (48 h) (MRC5). The Zn(II) **8** complex has a concentration-dependent hazardous impact. To two cancer cell lines, the Zn(II) 2-((*p*-tolylamino) methyl) phenolyl dithiocarbamate complex posed a similar

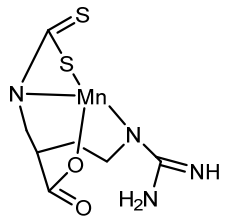
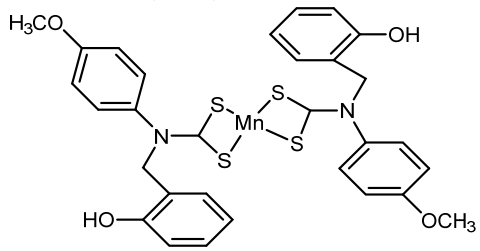
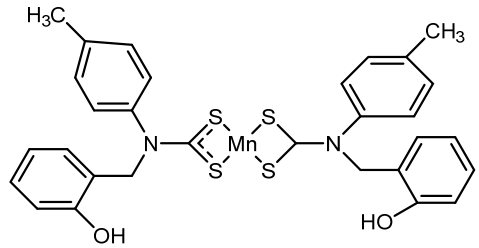
potential for harm (48 h) (HeLa and MRC5-SV2). In HeLa, MRC5-SV2, and MRC5 cells, Zn(II) 2-((*p*-tolylamino) methyl) phenolyl dithiocarbamate was determined to be 28.1, 19.8, and 22.3 µg/mL, respectively. Zn(II) was discovered to have a SI of 1.1. The MRC5-SV2 cancer cells were more vulnerable to the Zn(II) complex than were healthy cells, indicating that cancer cells were more vulnerable to its toxicity (MRC5) [53].

The coordination of the Zn(II) **9** complex with DNA was demonstrated by molecular docking data. At the IC_{50} value of 360.10 µg/mL, the cytotoxic activity of Zn(II)prolinethiocarbamate against the MCF-7 cell line indicated a change in the morphological structure of cancer cells. The Zn(II)prolineditiocarbamate complex can be a potential new alternative drug in the discovery of chemotherapeutic agents with potency and efficacy against the MCF-7 cell line [54].

■ CYTOTOXIC ACTION OF Mn(II) DITHIOCARBAMATE COMPLEXES AGAINST A RANGE OF CANCER CELL LINES

The cytotoxicity of several Mn(II) dithiocarbamate complexes against various cancer cell lines is displayed in Table 2. The Mn(II) **1** complex was identified as being active against cancer cells because its IC_{50} value showed a link between its cytotoxic activity and a positive control, cisplatin. The Mn(II) argininedithiocarbamate complex was more effective against MCF-7 cancer cells, when compared to the active compound from *Dioscorea esculenta* L. [55,57]. The Mn(II) complex is classified as moderately cytotoxic according to the IC_{50} standard for cytotoxic samples because the IC_{50} value falls between 100 and 1000 µg/mL [55,58]. The bioactivity of metals in the body and the structural characteristics of the complexes can both be used to observe the cytotoxic

Table 2. Cytotoxic action of Mn(II) dithiocarbamate complexes against a range of cancer cell lines (2020-2021)

Mn(II) dithiocarbamate complexes	Cancer cell line type	IC_{50} µg/mL	Main mechanism	Ref.
Mn(II) arginine dithiocarbamate 	Breast MCF-7	211.53	Inhibits cell mutation process by binding to guanine from MCF-7 cancer cell DNA	[55]
Mn(II) methoxyphenyl dithiocarbamate 	Lung MRC5-SV2	31.5	Induces apoptosis, DNA targets	[49]
Mn(II) 2-((*p*-tolylamino) methyl)phenolyl dithiocarbamate 	HeLa MRC5-SV2 MRC5	45.6 37.7 29.9	DNA targets	[53]

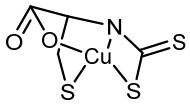
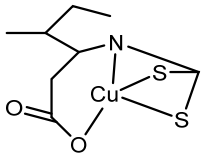
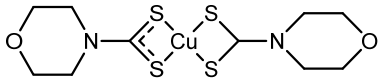
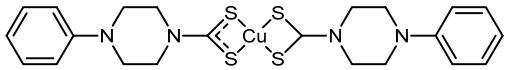
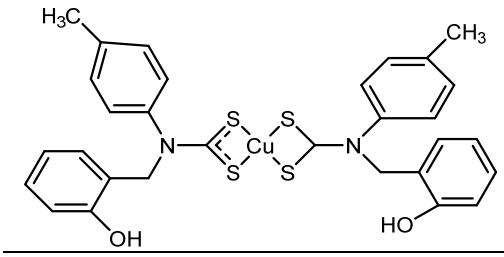
activity of the ligands. Mn(II) **2** complex had the same cytotoxic activity against MRC5-SV2 and MRC5 with SI of 0.8 [49]. For HeLa, MRC5-SV2, and MRC5 cells, the least toxic Mn(II) **3** complex (treatment time 48 h) had IC_{50} values of 45.6, 37.7, and 29.9 µg/mL, respectively [53].

■ Cu(II) DITHIOCARBAMATE COMPLEXES HAVE CYTOTOXIC ACTIVITY AGAINST A VARIETY OF CANCER CELL LINES

The cytotoxic efficacy of various Cu(II) dithiocarbamate complexes against several cancer cell types is shown in Table 3. The cytotoxicity test of Cu(II) **1** complex on MCF-7 cells yielded IC_{50} values, demonstrating a good association between Cu complexes (IC_{50} = 639.35 µg/mL) and cisplatin (IC_{50} = 470 µg/mL). As a result, this complex promotes morphological alterations in cancer cells as well as apoptosis. In the DNA double helix, the complex binds to the N(7) on guanine. The bond formed with DNA is covalent. Metal ions can produce intra-strand crosslinks between two strands of DNA, joining the two DNA strands into a double helix. Through the process of mitosis, this intra-strand cross-link damages cells, causing the tumor to stop growing. Tumor cells become hard as a result of metal ion cross-linking, making them unrecognizable and preventing DNA repair [45].

The Cu(II) **2** complex had an IC_{50} of 98.17 µg/mL in a cytotoxicity assay on MCF-7 cells, while cisplatin (IC_{50} = 50 µg/mL) was used as a control. These results show that the Cu complex's IC_{50} value is very near to that of cisplatin, indicating that it can be used as a reference for anticancer medications with few side effects. Cancer cells can be killed by the Cu(II) isoleucineedithiocarbamate complex, which changes morphology with increasing

Table 3. Cytotoxic action of Cu(II) dithiocarbamate complexes against a range of cancer cell lines (2018-2021)

Cu(II) dithiocarbamate complexes	Cancer cell line type	IC_{50} µg/mL	Main mechanism	Ref.
Cu(II)cysteine dithiocarbamate 	Breast MCF-7	639.35	Inhibits cell mutation process by binding to guanine from DNA	[45]
Cu(II)isoleucine dithiocarbamate 	Breast MCF-7	98.17	Inhibits cell mutation process by binding to guanine from DNA	[46]
Cu(II)morpholinyldithiocarbamate 	Renal TK-10 Melanoma UACC-62 Breast MCF-7	4.64 4.47 4.37	The bond form is similar to cisplatin, which is very strong irreversibly binds to DNA	[48]
Cu(II)bis(1-phenylpiperazine dithiocarbamate) 	Renal TK-10 Melanoma UACC-62 Breast MCF-7	19.83 3.34 17.52	DNA targets	[52]
Cu(II) 2-((*p*-tolylamino) methyl)phenolyl dithiocarbamate 	HeLa	30.1	DNA targets	[53]

Cu(II) complex concentration [46]. When compared to the cytotoxicity of parthenolides, the Cu(II) **3** complex demonstrated comparable efficacy against TK-10 and MCF-7 [48].

Cu(II) **4** complex inhibited the growth of UACC-62, MCF-7, and TK-10 cancer cell lines at IC_{50} concentrations of 3.34, 17.52, and 19.83 μg/mL, respectively, whereas Zn(II) complex inhibited the growth of MCF-7, TK-10, and UACC-62 cancer cell lines at IC_{50} concentrations of 8.42, 13.40, and 15.14 μg/mL, respectively. The platinum complex, in comparison to the platinum complex, was active at a concentration of 100 M (IC_{50}). Because copper is a necessary element with high biological activity, the Cu(II) bis(1-phenylpiperazine dithiocarbamate) complex inhibited growth [52]. The poisonous impact of the Cu(II) **5** complex is concentration-dependent. The MRC5 cell line was more hazardous to Cu(II) complexes. Cu(II) had IC_{50} values of 30.1, 17.9, and 14.0 μg/mL, respectively, for the effect (48 h) on HeLa, MRC5-SV2, and MRC5 cells. Cu(II) 2-((*p*-tolylamino) methyl) phenolyl dithiocarbamate had an SI of 0.8. It was discovered that MRC5-SV2 was less toxic than Cu(II) complexes to MRC5 [53].

■ Ni(II) DITHIOCARBAMATE COMPLEXES HAVE CYTOTOXIC ACTIVITY AGAINST A VARIETY OF CANCER CELL LINES

Ni complexes have been noted as possible anticancer drugs, however, thorough investigations of the cellular mechanism of action and anti-CSC (cancer stem cell) capabilities have not been widely conducted [59]. Based on *in vitro* studies, Ni(II) complexes with semicarbazone and thiosemicarbazone ligands have strong antiproliferative activity, and their cytotoxic effects are thought to be induced by damaging genomic DNA or inhibiting topoisomerases. Ni(II) complexes containing semicarbazone and thiosemicarbazone ligands exhibit strong antiproliferative activity *in vitro* and are thought to induce their cytotoxic effects by damaging genomic DNA or inhibiting topoisomerases [60].

The Ni(II)-tetraazamacrocyclic compound showed promise *in vitro* activity against promyelocytic leukemia HL-60 and hepatocellular carcinoma BEL-7404 cell lines. This complex is thought to cause apoptosis by clumping and condensing chromatin and interfering with cell cycle progression. Based on *in vitro* studies, Ni(II) complex containing the *N*-aroyl-*N*'-thiohydrazide ligand inhibits lymphoma (DL) growth, and in DL-bearing mice [61]. A more recent study demonstrated that the Ni(II)-pyrithione complex was able to inhibit the proliferation of cultured tumor cells, primary cells from acute tumors of human myeloid leukemia patients, and chronic myelogenous leukemia K562 and lung carcinoma A549 xenografts in naked mice [62].

The IC_{50} value of the Ni(*N*,*N*-dithiocarbamate)2 (4,7-diphenyl-1,10-phenanthroline) complex was 11 times lower than the IC_{50} value of cisplatin in MB-231 adenocarcinoma MDA cells of the breast. Ni(*N*,*N*-diethyldithiocarbamate)2(1,10-phenanthroline), Ni(*N*, *N*-diethyl dithiocarbamate)2(3,4,7,8-tetramethyl-1,10-phenanthroline), Ni(*N*,*N*-dithiocarbamate)2(3,4,7,8-tetramethyl-1,10 phenanthroline), Ni(*N*,*N*-dithiocarba (*N*,*N*-diphenyl-1, 10-phenanthroline). The combination containing diethyldithiocarbamate, on the other hand, demonstrated a 2-fold selective efficacy for CSCs [63].

■ METAL COMPLEX MECHANISM AGAINST CANCER CELL LINE

Differences in cytotoxicity of several complex compounds against cancer cell lines MCF-7 can be explained by the nature of the metal's bioactivity in the body and the structural properties of the complex. The Zn complex is linked to the Zn(II) complex's strong cytotoxic effect because it inhibits heme oxygenase (HMOX1), which is produced in substantial amounts in solid tumors [64]. The nature of the bioactivity of the metal itself in the body and the structural features of the complex can be used to explain the different cytotoxicity of various complex compounds. The strong coordination between the Zn(II) complex and DNA is associated with the concept of HSAB. Denaturation of DNA can be caused by Zn(II) ions attaching to it. When DNA interacts with zinc, it causes a shift in the absorption spectrum as well as increased denaturation. This shows that Zn-DNA can also be made in physiological conditions. In eukaryotic cells, this can

alter a range of biochemical processes and pathways [65].

When viewed through the HSAB point of view, Cu(II) metal's HSAB properties, which are classified as borderline acids, and the nitrogen group of guanine, which is the basic framework of DNA structure, are classified as borderline bases, allowing the complex Cu(II) to form a strong bond with the nitrogen bases of the basic framework of DNA structure. And it's backed up by the fact that Cu is a vital element with the potential to bioactivate in the human body [23].

Mn complexes show good coordination with DNA based on the HSAB principle. Mn metal is also a necessary metal that transforms into a bioactive element in the human body and lessens toxicity. Additionally, the cytotoxicity of the Mn(II) complex was raised and the ligand was intercalated into the DNA gap thanks to the arginindithiocarbamate ligand utilized as a scaffold in the complex production. The connections between the Mn complex and DNA prevent cancer cells from entering the mitotic phase as a result [53,66]. Metal complexes can also be intercalated (entered) into the spaces between the DNA double helix's base pairs. The majority of these reactions, however, take place in complexes with planar aromatic heterocyclic ligands [67].

DNA can be bound to metal complexes covalently or noncovalently. The initial non-covalent interaction is

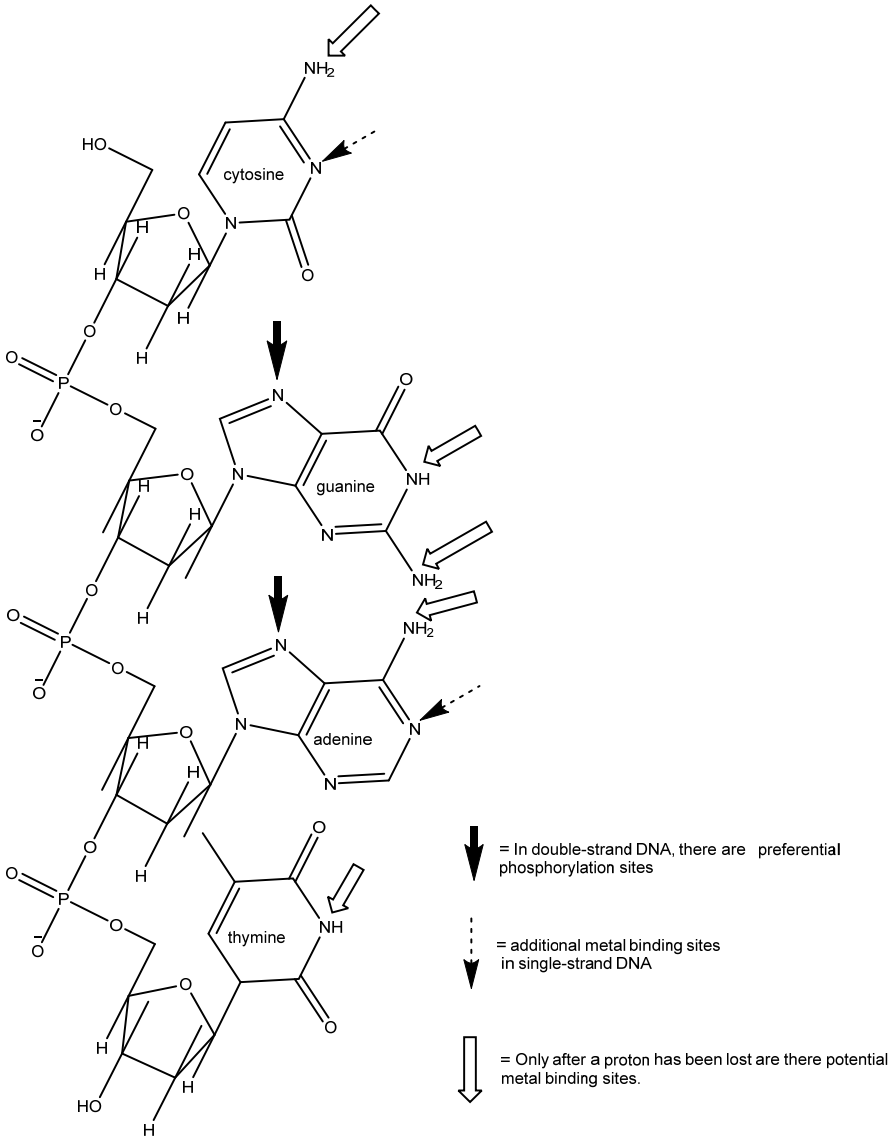


Fig 1. Possible metal complexes binding sites on DNA (adapted from ref. [73])

of its most fundamental type when it comes to outside binding, also known as electrostatic touch. This interaction occurs between the metal complex and the negatively charged DNA outer skeleton. Groove bonding is another form of interaction, such as van der Waals forces, hydrogen bonding, and the hydrophobic effect.

Based on the findings of this research, it was seen that there was an effect of the ligand in increasing the cytotoxicity of the complex against cancer cells. The considerable disparity in IC_{50} values found between metal complexes and metals without ligands demonstrates this. The IC_{50} value found in all metal complexes was significantly lower than that of the metal without the ligand. This procedure permits ligands to be intercalated between DNA base pairs. As a result, metal complexes can be classified as both covalently and non-covalently bound. Fig. 1 depicts the interaction between metal complexes and DNA.

Purine nucleobases (N7) of DNA are the main and most common targets in studying metal complex interactions and DNA [74]. Fig. 1 depicts a schematic of how metal complexes bind to DNA's active sites. In double-stranded DNA, N3 is sterically hindered, leaving just N7 (bold arrows in Fig. 1). In single-stranded DNA, N1 adenine and N3 cytosine can both bind to Zn complexes (dotted arrows in Fig. 1). Since aromatic systems' protonated purine and pyrimidine nitrogen atoms have delocalized lone pairs of electrons, they can only be exploited for Zn complex coordination after deprotonation (empty arrow in Fig. 1). In guanine bonds, there is more kinetic energy [75]. The enhanced basicity of nitrogen is what gives rise to this propensity. Lower melting temperatures, shortening, separation, and denaturation have all been noted as a result of the DNA structure being significantly altered. According to their morphology, MCF-7 cells' cell cycle progression was hampered by the Zn(II)-DNA complex reaction. If the damage is not sufficiently repaired, the cell will eventually try to go through mitosis but will fail, dying as a result of apoptosis.

■ CONCLUSION AND RECOMMENDATION

The dithiocarbamate essential metal complex was able to cause cancer cell death through apoptosis in all complexes. Some of the complexes have more cytotoxic activity than the reference medicines against several cancer cell lines (T47D, MCF-7, TK-10, UACC-62, MRC5, MRC5-SV2, and HeLa). The MTS assay has been utilized to study the majority of its anticancer activity, with IC_{50} values that are equivalent to or even lower than those of currently used therapeutic medicines, particularly cisplatin. The great majority of DNA cases are the principal objectives. As a result, we believe that essential metals complexed with dithiocarbamate could be a game-changer in the development of cancer treatments. The structural structure of metal complexes in biological systems and cells influences their reactivity. The biological effects of complexes with more alkyl and aryl groups linked to the metal core are better than those with less alkyl and aryl groups. More lipophilic complexes, such as those with high phenyl groups, have been discovered to readily interact with the cellular membrane and cytoplasm, resulting in increased permeability within cells and cell death. More research on the long-term stability and sustainability of the dithiocarbamate essential metal complex, as well as its anti-cancer capabilities, is needed, as this is a vital component in its future usefulness.

■ ACKNOWLEDGMENTS

We thank the funders, Center for Education Financial Services (PUSLAPDIK) and the Education Fund Management Institute (LPDP) with contract number 0553/J5.2.3/BPI.06/10/2021.

■ AUTHOR CONTRIBUTIONS

Rizal Irfandi, Indah Raya, Ahyar Ahmad, and Ahmad Fudholi designed research ideas, conducted reviews and wrote manuscripts. Hasnah Natsir, Harningsih Karim, Santi, and Subakir Salnus did the review and editing.

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