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Experimental Research

Potential anticancer activity of Mn (II) complexes containing arginine dithiocarbamate ligand on MCF-7 breast cancer cell lines

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ABSTRACT

Introduction: Cancer refer to genetic changes in the DNA structure accompanied by abnormal growth of normal cells, and resulting in the death of these structures, and is a disease currently recognized as a major cause of mortality globally. Chemotherapy plays important role in breast cancer management. Non-toxic metals have been developed to replace the highly toxic cisplatin, an example being Manganese. Furthermore, Ligands have displayed great capabilities in the determination of anticancer properties, and an essential agent exploited in drug development is arginine dithiocarbamate. Therefore, this study was conducted to examine the anticancer potentials of Mn (II) arginine dithiocarbamate.

Methods: The synthesis and spectroscopic analysis of the Mn (II) Arginine dithiocarbamate complex was successfully carried out. Then, the complexes were characterized through the employment of the UV-Vis, FT-IR, as well as the melting point tests, and subsequently analyzed for anticancer activities through in vitro means. The compound was produced from UV-Vis spectrum at 246 and 385 nm wavelengths and IR spectrum at wave numbers 354-499 cm^{-1}.

Results: The results revealed the cytotoxicity of Mn (II) Arginine dithiocarbamate against the MCF-7 cell line, observed from a significant change in the morphology of the cancer cells with IC50 value of 211.53 μg/mL.

Conclusion: The compound, Mn (II) Arginine dithiocarbamate has effective anticancer potentials against MCF-7 cancer cells.

1. Introduction

Cancer occurs as a result of changes in DNA resulting in uncontrolled cell growth [1,2]. This disease became the second leading cause of death globally in 2015 [3], with breast cancer presenting with the highest incidence in Indonesia in 2013 at a prevalence of 0.5%, according to the data compiled by the 2013 Basic Health Research. Also, this form of cancer generates the highest number of new cases, based on the data provided by Dharmais Cancer Hospital for four years, with 819 patients and 217 deaths, and these figures are on a continuous rise [4].

Consequently, the interaction of metal complexes with DNA has attracted abundant attention in research world, and similar to the application in medicine, photodynamic therapy (PDT) is a cancer healing method with favorable prospects [5]. Mn (II) metal is an essential metal which is widely used in the body as a cofactor in several enzymes [6]. Arginine is an amino acid that is needed by the body to run metabolism [7]. Dithiocarbamate also in the body has less toxicity [8]. These three reasons make the use of Mn (II) in combination with the arginine thiocarbamate ligand in cancer therapy to have very less side effects or complications. Coordination of Mn (II) with emodin can increase anticancer activity. The complex can cause changes in cell morphology, reduce the percentage of viability, and induce G0/G1 phase capture and apoptosis in cancer cells [9]. Based on UV-Vis and IR spectroscopic studies that Mn (II), forms complexes with DNA. The interaction of the Mn complex with DNA takes place through hydrogen bonds involving hydrogen bonds [10].

Dithiocarbamate is a uniquely structured compound, owing to the presence of S group as both a monodentate and bidentate electron donor. These compounds bond predominantly with transition metals to form complexes, an example seen with manganese metals [11–13].

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Meanwhile, the use of these ligands with arginine as an additional donor increases the diversity of the complex structure, and also influences the biological activity [14]. The dithiocarbamate class of metal complexing compounds has become a new class of proteasome anticancer inhibitors with great potential to overcome the limitations seen with the use of bortezomib [15]. Dithiocarbamates are a class of metal chelating compounds with various applications in medicine. Ditiocarbamate has been used for the treatment of bacterial and fungal infections, possibly the treatment of AIDS, and most recently cancer. Chemotherapy agents are currently highly toxic and therefore their efficacy in eradicating tumors is very limited. As a result many scientists have joined in the search for new targeted therapies with the hope of reducing toxicity while maximizing their potency and proteasome inhibition has become an interesting therapy in this regard. Here we discuss the origin, mechanism, and evolution of dithiocarbamates as potent proteasome inhibitors and therefore anti-cancer agents [15,16]. Coordination based on dithiocarbamate compounds as a potent proteasome inhibitor in human cancer cells. Thus, this approach could pave the way for the development of nontoxic anticancer therapies [16].

Complications from use are not yet known, because this is only stage 1 in vitro research, then stage 2 research will be carried out in animals, and finally stage 3 in humans. Mn (II) arginine dithiocarbamate complex is predicted to have low side effects when compared to cisplatin because the metal raw material used in this study is an essential metal and has biological activity in the body. For this reason, this study uses the generally environmentally-friendly and minimally toxic Mn (II), in combination with the ligand arginine dithiocarbamate, as potential candidates in tumor/cancer therapy. Furthermore, biologically active complexes have garnered extensive attention as inclusions in the design of potential antitumor agents [17]. Also, dithiocarbamate ligands are known to be medically beneficial, and are utilized as radio target in the chemotherapy of tumors [18,19].

Therefore, this research aims to characterize the synthesized Mn (II) arginine dithiocarbamate complex and examine the compound's anticancer activity against MCF-7 cell line, and the analysis outcomes were determinants of the compound's anticancer efficacy.

2. Methods

2.1. Materials

CS_2 99.5% (Ajax Chemical Ltd), Cisplatin, Roswell Park Memorial Institute Medium, DMSO, Mangane(II)sulphate, cystein PA, 95% Ethanol, 95% methanol, 95% Acetone, 95% n-hexane, and 95% Acetonitrile (Central Laboratory of Hasanuddin University, Indonesia). MCF-7 were tested at Padjadjaran University.

Synthesis of Mn (II) Complex Compounds with arginine dithiocarbamate ligand.

A mass of 0.5095g $MnSO_4 \cdot H_2O$ (3 mmol) was placed in an Erlenmeyer glass, and made into a solution with 10 mL of ethyl alcohol (solution 1), accompanied by 0.9001g (5 mmol) of Arginine, and a subsequent dissolution with 10 mL of ethanol. Then, 0.302 mL (5 mmol) CS2 solution was added to solution 1 slowly at cold temperature, and combined with a magnetic stirrer for 30 min (solution 2). Additionally, the resulting precipitate was filtered and placed in a desiccator to facilitate dehydration, and then crystallized with a solvent prepared from an acetonitrile and ethanol blend (1: 2, v/v), to obtain pure crystals to be further analyzed and characterized (Fig. 1).

2.2. Characterization of Mn (II) arginine dithiocarbamate complexes

The ligands were physically characterized by the implementation of melting point and conductivity tests, as well as chemically by UV-Vis and FT-IR spectrophotometric assays.

2.3. Cytotoxicity test against cancer cell lines

The sample solutions of the complexes at various concentrations, alongside cisplatin (IC_{50} = 5.7 μg/mL) used as a positive control were added to the MCF-7 cells and subsequently incubated for 24 h. Then, the resulting mixture was added to the dye reagent and re-incubated for another 4 h at 37 °C. Consequently, the number of HeLa cells inhibited by the test sample after uptake was measured by the use of a multimode reader at λmaks (570–600 nm) after the inclusion of stop solution reagents. Furthermore, the IC_{50} values were calculated by the extrapolation of the 50% line produced by the uptake of the positive control on the absorption curve at various sample concentrations.

2.4. Preparation of media, positive control and arginine dithiocarbamate complex

The liquid culture media was prepared at the Roswell Park Memorial Institute Medium (RPMI) by the combination of 10% Fetal Bovine Serum (FBS) and 50 μL/50 mL antibiotics, with Cisplatin as the positive control. Meanwhile, the stock was prepared by the dissolution of cysteine dithiocarbamate complex in the nontoxic solvent, DMSO at a series of strengths. Furthermore, the antiproliferation assay work solution used was the Presto Blue™ Cell Viability Reagent.

2.5. Preparation of MCF-7 cells

The MCF-7 cells were confluent at 70%, discharged onto media dish, and doused with 1 mL *Phosphate Buffered Saline* (PBS) two times, followed by 1 ml Trypsin-EDTA solution added into the dish, and then

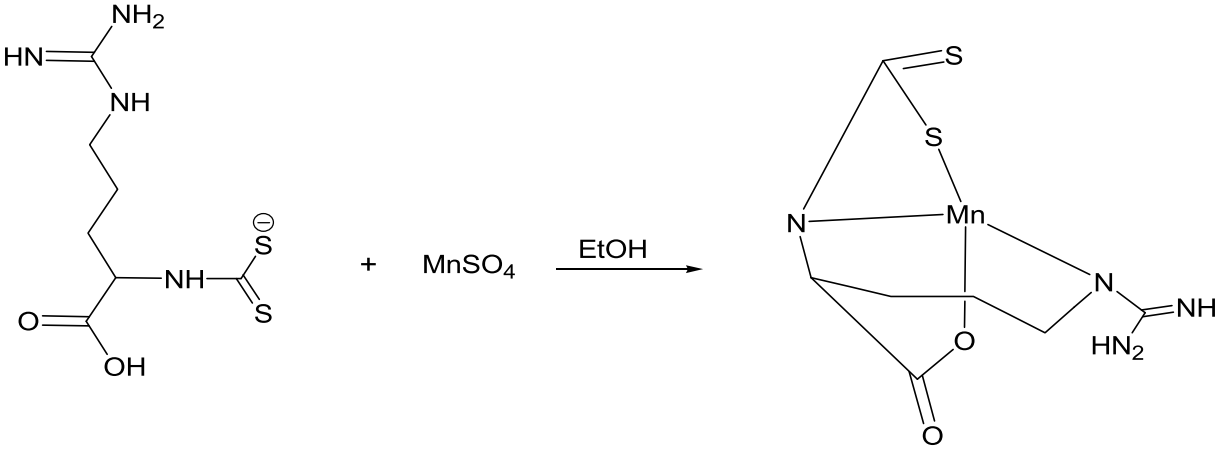

Fig. 1. Synthesis reaction of Mn (II) arginine dithiocarbamate.

incubated for 5 min. Furthermore, the cell layers were dispersed, and appeared to float when viewed with the inverted microscope. Finally, the cells were inserted into a tube containing growth media, rotated at 3000 rpm for 5 min, the supernatant subsequently disposed, and the resultant pellets dissolved in a tube of media.

2.6. Seeding cells into 96 well plates

The cell count and viability were performed with trypan blue exclusion, and then resuspended to produce a final density of 170,000 cells/mL in the media. (17,000 cells/well). Meanwhile, 10 μL of trypan blue was prepared in sterile microtube, 10 μL of the cell suspension added to the solution and subsequently homogenized. Then, the hemocytometers and the lids were cleaned with the use of 70% ethanol, dried, and 10 μL of the trypan blue cell solution inserted slowly into one of the chambers with the use of a pipette. Finally, the number of viable cells per mL was determined, the cell cultures seeded into 96 well plates, incubated for 24 h or until a minimum of 70% confluent cells at 37 °C and 5% CO_2 gas were observed.

2.7. Cell treatment with positive sample/positive control/negative control

A total of eight 1.5 mL microtubes were prepared, with each container labeled with the appropriate dilution strength, and the sample stock diluted into eight corresponding concentration variants with the use of a media solvent. Then, 96 well plates containing cells from the incubator were collected and labeled along the left margins according to the rows to be treated by the standard or sample. In addition, the media was discarded from each well. Then, 100 μL of each sample, along with the cisplatin control in the microtubes were transferred into each of the corresponding wells on the 96 plates containing the cells with the use of a micropipette and subsequently re-incubated for 24 h.

2.8. Provision of Presto Blue reagents and absorbance measurements

A volume of 9 mL of media from each tube was added to 1 mL of "Presto Blue™ Cell Viability Reagent" (10 μL of reagent for 90 μL media), and then 100 μL of the resulting mixture inserted into each well. After this, the microplates were incubated for 1–2 h until discoloration occurred. On entrance into the viable cell, the indicator was transformed from the non-luminous resazurin blue, into the highly fluorescent resorufin counterpart. The converted values were proportionate to the living cell count, and the absorbances were consequently capable of quantitative measurement, as the absorbance spectrum was utilized for resazurin and resorufin. Finally, these values were estimated at a wave length of 570 nm (reference: 600 nm) using a multimode reader.

3. Results

The yield of the Mn(II) arginine dithiocarbamate compound synthesized was 28.39%, and the melting point estimated between 202 °C–204 °C.

3.1. UV-Vis characterization

The complex characterized by UV-Vis spectrophotometers displayed several wavelengths as illustrated in Table 1. Furthermore, the absorption at 385 nm was representative of the transition of electrons from the orbital n → π* in the group N = C = S. Meanwhile, the wavelength of 246 nm indicated a transition from the orbitals π → π* in the group CS_2, attributable to the hyperconjugation effect experienced by the R group. The spectral outcomes of the synthesized ligand are shown in Fig. 2.

Table 1
The Wavelength of Mn (II) arginine dithiocarbamate.

Compound	λ Maximum (nm)	Electronic Transition
Mn(II)argnininedithiocarbamate	246	π→π*
	385	n→π*

3.2. IR characterization

A single bond group v (C - N) exists in the dithiocarbamate complex at the wave number between 1350 and 1250 cm^{-1} and v (C = N) at 1690 - 1640 cm^{-1}. Meanwhile, the C - S bond group occurs at wave numbers 550–800 cm^{-1}, and the C = S at 1050-1200 cm^{-1} [11]. Furthermore, the bonds between the metal and the ligands are observable from the far infrared absorption ranging from the wave number 400-100 cm^{-1}, as seen in the linkages formed between sulfur or nitrogen and metals [12].

Also, the metal coordination bonds with ligands are identifiable from the resulting spectrum as observed in Table 2. Subsequently, the interactions between the Mn bond and the S group were detected at wave number 354 cm-1, with the O atom at 445 cm^{-1} and finally, the N atom at 499 cm^{-1}. In addition, the C = N double bond was identified from the spectrum with the wave number 1645 cm^{-1}, while the C = S double bond coordinating with Mn ion was observed at 1116 cm-1. Furthermore, Fig. 3 shows the FT-IR spectrum of the complex compound, with each compound having a specific absorption in the infrared spectrum dependent on the metal and ligands.

3.3. Cytotoxicity test on MCF-7 cells

The IC_{50} value of the complex was determined from the regression equation y = −0.0016x + 0.6826 (Fig. 4), obtained by replacing the value of y with half the value of the control (DMSO). Subsequently, the well plate documentation results of Mn (II) arginine dithiocarbamate, as well as the comparison of sample concentrations with media + cells, alongside cisplatin for MCF-7 are displayed in Fig. 5. Also, the IC_{50} of the sample were evaluated due to similarities of the color to cisplatin, and the value obtained between 125 and 250 μg/mL.

The apoptosis of MCF-7 cells against cisplatin and a sample of the complex are illustrated in Fig. 6, and this phase was dependent on the concentration and nature of the inhibitory substance. Subsequently, in the concentration of the sample variant from 7.81 to 62.5 μg/mL, no visible cell death was observed, and this phenomenon was capable of associated to the image of the initial cell media that remained normal without treatment. Therefore, apoptosis commenced at the 125 μg/mL concentration sample, after an addition of cisplatin to the media. Also, the MCF-7 cells experienced late apoptosis at higher concentrations.

4. Discussion

Metals exhibit distinct features comprising redox activity, several coordination structures, and reactivity towards organic compounds. As a result of this function, these elements typically undergo strict regulations, and abnormal ionic strengths are affiliated with numerous diseases, including cancer [13]. Therefore, metal complexes, either as drugs or prodrugs, have become very promising anticancer candidates [14,20,21]. Also, the use of metals and the corresponding salts for medicinal purposes, from iatrochemistry to contemporary medicine, has existed from time immemorial [21,22]. Consequently, the invention of cisplatin, cis-[Pt (II) (NH(3))(2) Cl (2)], was a breakthrough and sparked interests in platinum(II)- and other metallic composites as prospective chemotherapeutic agents [13].

Moreover, transition metals including copper, iron, and manganese, and so on, are linked with many biological processes, including electron transfer and catalysis, as well as fundamental functions, and are therefore regularly involved with the binding sites of biological polypeptides [23,24]. Manganese (Mn) is an essential trace metal indispensable in enzyme functionality, for instance, arginase, glutamine synthetase, and Mn-superoxide dismutase activity [25]. Furthermore, this metal is able to assume various valence forms, and limited data suggest the

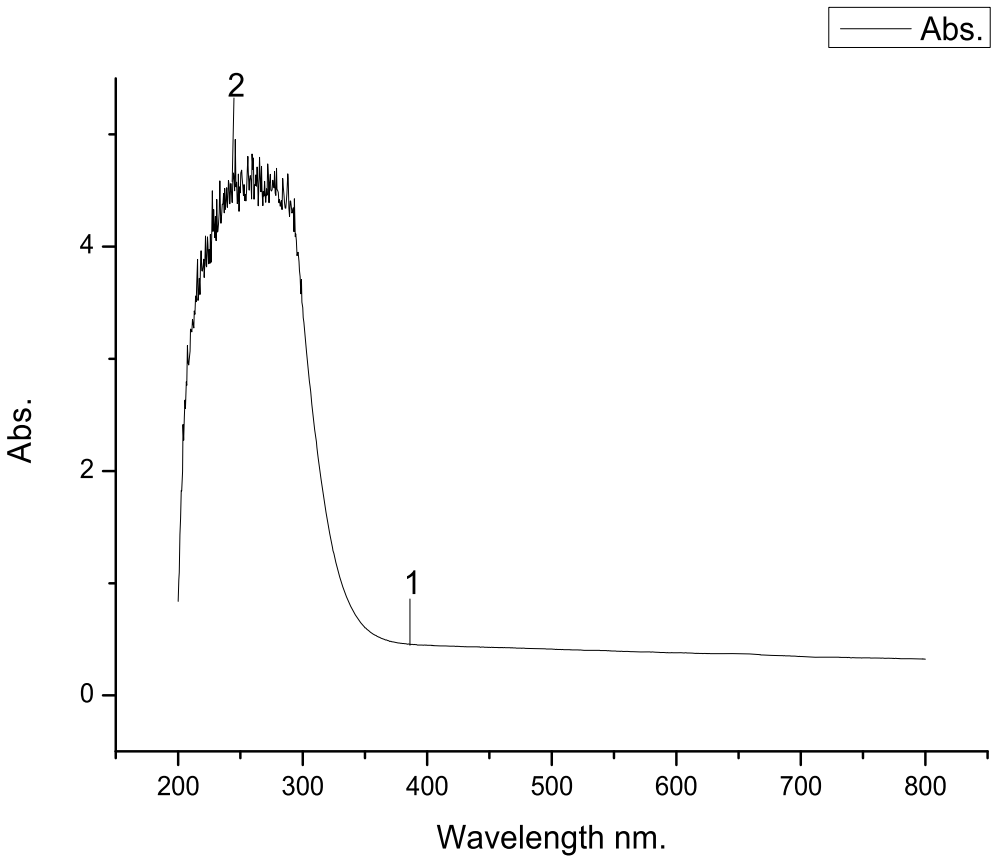

Fig. 2. UV-Vis Spectrum of Mn (II) arginine dithiocarbamate.

Table 2
IR data of Mn (II) arginine dithiocarbamate.

Compound	v(C═N)	v(C═S)	v(M − S)	v(M − O)	v(M − N)
Mn(II)ArgDtc	1645 s	1116 m	354 w	445 w	499 w

s = strong; m = medium; w = weak.

propensity to undergo oxidative modifications whilst in the body [26,27]. Despite the normal oxidation number of the ion in enzymes being Mn(III), majority of manganese intake from diet and other circumstances are either Mn(II) or Mn(IV) [27]. This metal is principal for the maintenance of the functionality, as well as biochemical and cellular modulation required by living organisms [28]. Also, the element is vital for growth and development, acts during the activation of immunity, blood glucose control, adenosine triphosphate (ATP) regulation, reproduction, digestion and skeletal growth [28,29].

In addition to tetraethylthiuram disulfide (DSF), diethyldithiocarbamate (DDTC) and pyrrolidine dithiocarbamate (PDTC) also belong to the dithiocarbamate group revealed as powerful metal sequestering agents [13,30–33]. DDTC was revealed to be capable of combining with copper to create a novel potent inhibitory complex of functions similar to proteasomal chymotrypsin, promote cell death, decrease androgen (AR) and estrogen receptor (ERα and ERβ) protein manifestation in malignant prostate and breast tissues [13]. Reports garnered further revealed PDTC, after linkage to copper, exhibited comparable activities on cultivated human prostate cancer cells, along with the suppression of proliferation [33]. Also, the anticancer activity of copper has been postulated to reflect in the manganese (II) arginine dithiocarbamate compound.

The cytotoxicity of the synthesized complex was tested in vitro against the MCF-7 cancer cells and compared with cisplatin, the most commonly used drug currently recognized as toxic to these cancer cells. From the results displayed on Table 3, the IC_{50} value of the Mn (II) complex was similar to the value of cisplatin, and hence, expressed as active against cancer cells. Furthermore, the cytotoxicity results of the complex were more effective against the cells (IC_{50} = 211.53 μg/mL) when compared to the IC_{50} value of 632.42 μg/mL produced by the semi-polar fraction of *Dioscorea esculenta* L. as reported by Haryoto [34].

According to the Prayong classification (2008) [35] regarding the IC_{50} standard for cytotoxic samples, the Mn (II) complex belongs to the medium cytotoxic category owing as the IC_{50} value occurred between 100 and 1000 μg/mL. In addition, the ligand's cytotoxic activities against the cell line are perceivable in terms of the bioactivity of metals in the body, as well as the complex structural properties. Also, the consideration of Mn (II) from the view of HSAB properties included in the category of borderline acids and Nitrogen groups from guanine, the basic framework of DNA included in the category of soft bases, permitted the formation of a strong bond between the complex and two DNA strands in a double helix. Furthermore, the nature of Mn, an essential element with bioactive capacities in the human body, compared to harmful cisplatin, depleted the toxicity. Subsequently, the high IC_{50} value of the Mn(II) complex was influenced by arginine dithiocarbamate ligands employed in the synthesis of complex compounds, and able to process ligand intercalation into DNA base pairs. Therefore, the propensity of metal complexes to not only covalently coordinate, but also bond non-covalently was affirmed, and this ion was able to interact with DNA through the formation of intra-strand cross--links [36]. Also, the resulting bonds prevented the mitotic phase of cancer cells, causing these structures to become stiff, deter reparation and induce cellular apoptosis.

Mn (II) metal complexes with arginine dithiocarbamate ligand have been successfully synthesized and characterized. And it shows that there has been coordination between the Mn (II) atom with Sulfur (S), Nitrogen (N) and Oxygen (O) from the arginine dithiocarbamate ligand.

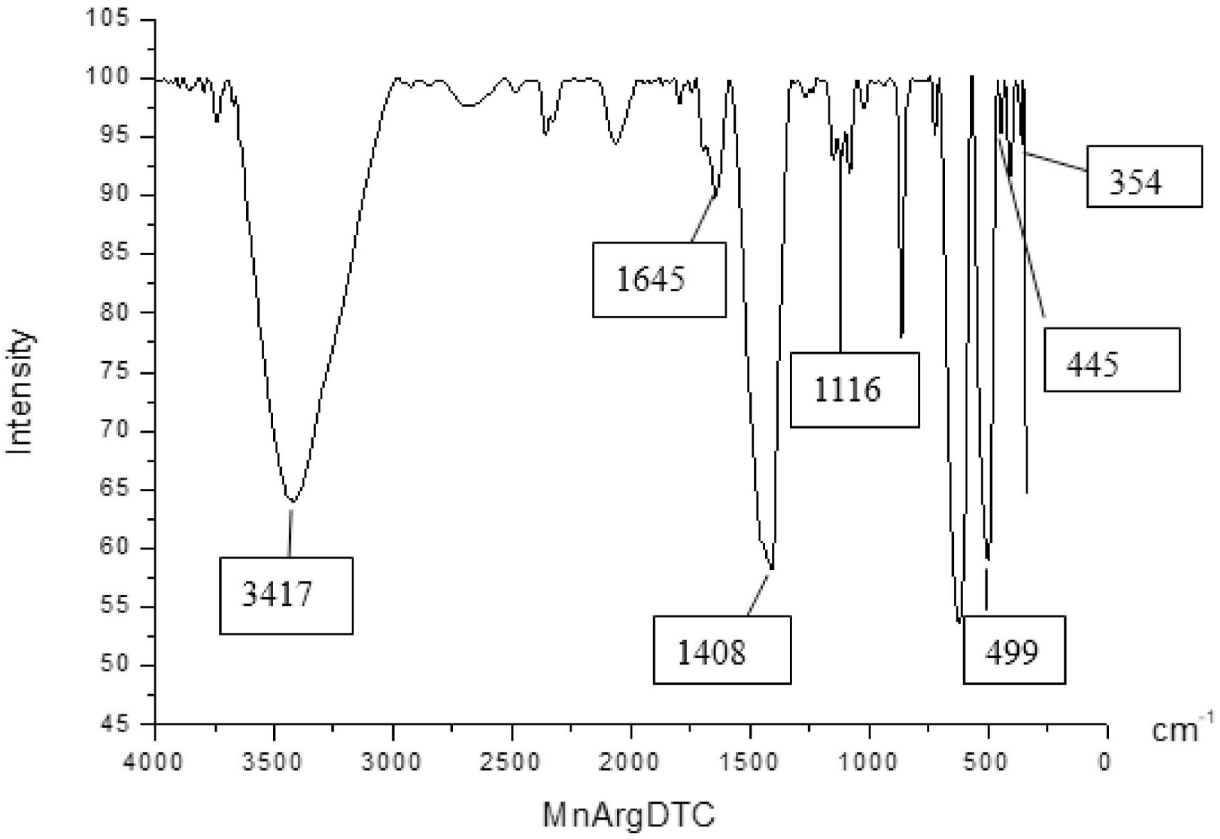

Fig. 3. IR Spectrum of Mn (II) arginine dithiocarbamate.

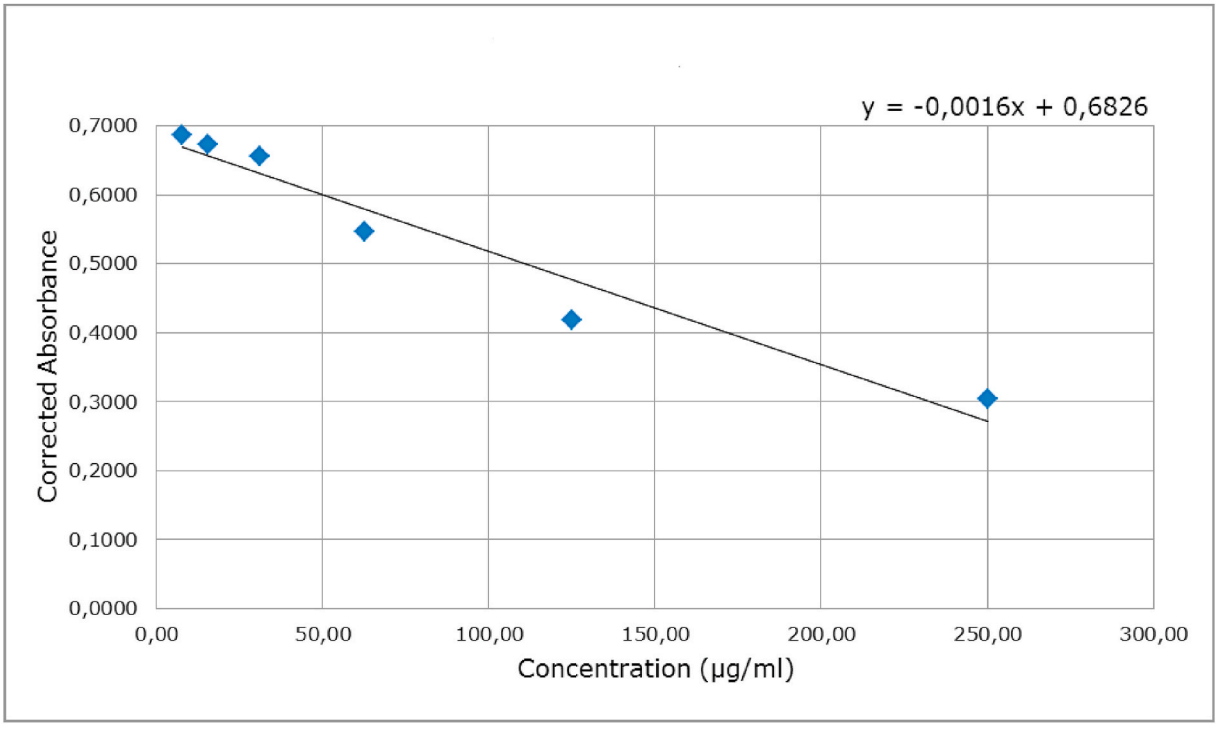

Fig. 4. Cytotoxicity Curve of Mn (II) arginine dithiocarbamate for MCF-7 cancer cells.

This complex can inhibit cancer cell proliferation in a way that depends on the concentration of the Mn (II) complex. Its IC50 value indicates that Mn (II) arginine dithiocarbamate has excellent inhibitory activity against MCF-7 cancer cells. In fact, the Mn (II) Mn (II) arginine dithiocarbamate complex can make cancer cells undergo apoptosis in vitro in a concentration-dependent way, which can inhibit the proliferation of

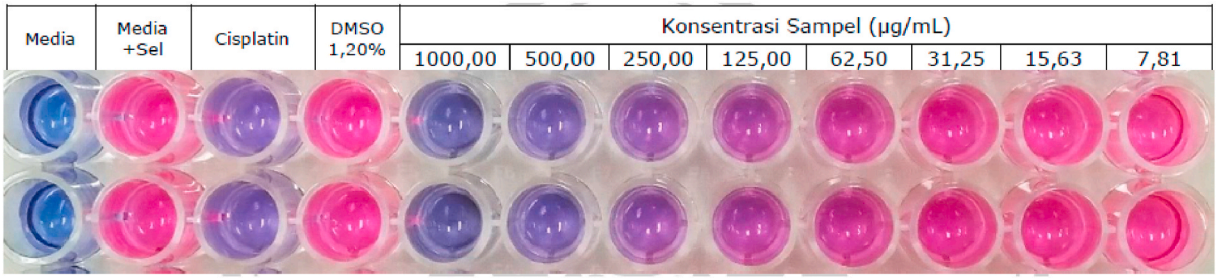

Fig. 5. Well Plate Documentation Test Results of Mn(II)arginine dithiocarbamate for MCF-7.

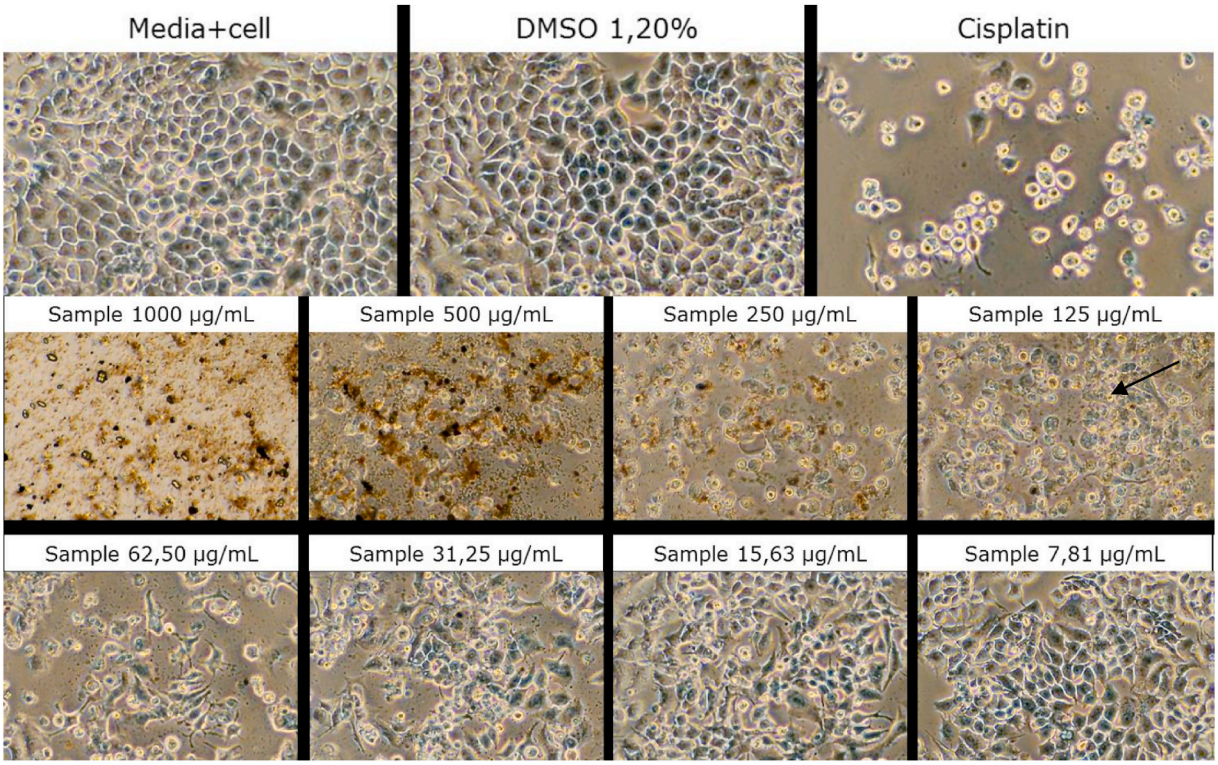

Fig. 6. Apoptosis of MCF-7 cells induced by Mn (II) arginine dithiocarbamate (arrow).

Table 3
IC_{50} values of the Mn (II) arginine dithiocarbamate Complexes.

Compounds	t (h)	IC_{50} (µg/mL)
		MCF-7
Mn(II)ArgDtc	48	211,53
Cisplatin	48	53,48

MCF-7 cancer cells [9]. Thus, the Mn (II) arginine dithiocarbamate complex could be a potential cancer drug.

The challenge faced in this study is the difficulty of finding a single solvent during the crystallization stage of the Mn complex, as for the solution by using a double solvent, namely acetonitrile and ethanol.

5. Conclusion

The Mn (II) arginine dithiocarbamate complex synthesis was performed by an in-situ method through an interaction between a primary amine (arginine) and carbon disulfide (CS_2) in ethanol, alongside the Mn metal solvents in the form of salts. In addition, the analysis of the Mn (II) complex against the MCF-7 cancer cell line revealed the existence of moderate cytotoxicity with IC50 = 211.53 µg/mL. It means Mn (II) Arginine dithiocarbamate has effective anticancer potentials against MCF-7 cell lines.

Provenance and peer review

Not commissioned, externally peer reviewed.

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