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Original Article

Synthesis, Spectroscopic, Biological Screening of Mn (II) and Cu (II) Complexes with Cysteine

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ABSTRACT

Objectives: Cysteine is a promising ligand for synthesizing complexes with Mn (II) and Cu (II) ions. The main objectives of the study were to synthesize, characterize and examine the Biochemical behavior of metal complexes. **Materials and Methods:** Metal complexes were synthesized by adding a methanolic solution of ligand (1 mmol) to manganese Chloride/Copper acetate (1 mmol). The resulting mixture was stirred magnetically for 4-5hr at room temperature. The complexes were then filtered, washed with ethanol followed by ether and dried. **Results:** The resulting complexes were investigated by the help of elemental analysis, Molar Conductance, IR, Electronic, NMR Spectral Studies and biological Studies. **Conclusion:** The transition metal complexes have been obtained by the treatment of Sodium salt of L-cysteine ligand with metal acetate/chloride. Complexes under investigation have shown antibacterial, antifungal and potential anticancer activities.

Keywords: Anticancer activity, Biocidal, Spectra, Synthesis.

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INTRODUCTION

Amino acids are the fundamental building blocks of Proteins which are organic molecules. They consist of an amino group ($-NH_2$), a carboxylic group and a unique side chain group for each amino acid (Jiang *et al*., 2022; Williams *et al*., 2024; Wu., 2009; De Koning, 2013; Sameem *et al*., 2018). L-cysteine is a non essential amino acid that is synthesized in the liver from methionine, an essential amino acid in humans (Carenzi *et al*., 2020) It contains an amino group ($-NH_2$) a Carboxylic group (-COOH) and a Sulphur atom in the form of thiol group (-SH). The thiol group is responsible for the amino acid's high reactivity and has been shown to have significant biological benefits in humans (Ma *et al*., 2021; Shemetov *et al*., 2012). The sodium salt of L-cysteine exhibits significantly expanded skills as an antioxidant, reducing agent and component of medicine, among other functions (Azad *et al*., 2017; Lee *et al*., 2021; Zhou *et al*., 2013; Juliano *et al*., 2011). Additionally, it significantly improves its ability to selectively target certain sites and greatly raises its efficiency in chemical processes (Tobias and Hemminger, 2008; Zhang and Cremer, 2010; Kim *et al*., 2012).The sodium salt of L- cysteine functions as a ligand capable of forming complexes have diverse uses in the fields of drug development and pharmaceutical industry research has indicated that cysteine is a biologically significant ligand that plays a role in the creation at different sites, such as Nitrogen and Sulphur (N,S), Oxygen and Sulphur (O,S) or Nitrogen and Oxygen (N,O) (Rosenberg *et al*., 1965; Rosenberg *et al*.,1969; Pucciarini *et al*., 2019). Due to its biological and chemical characteristics, cysteine is a promising ligand for synthesizing complexes with bioactive metals such as cobalt, nickel and copper. Cysteine has been utilized as a coligand ranitidine, which is the most effective medication for treating peptic and duodenal ulcers (Go *et al*., 2015; Meyer and Hell, 2005).

MATERIALS AND METHODS

Materials

All the compounds utilized were of analytical reagent grade and the solvents were dehydrated and purified prior to usage in accordance with established protocol. The organic solvents DMSO, DMF, Ethanol and Ether were of analytical reagent quality and were utilized without any additional Purification.

Methods

Synthesis of Complexes

Metal complexes of $Mn[C_3H_5NO_2S]$ and $Cu[C_3H_5NO_2S]$ were synthesized by adding a methanolic solution of the ligand $[C_3H_6NO_2SNa]$ (1 mmol) to manganese Chloride/Copper acetate (1 mmol). The resulting mixture was stirred magnetically for 3-5 hr at room temperature. (Scheme 1) The complexes were then filtered, washed with ethanol and ether and dried.

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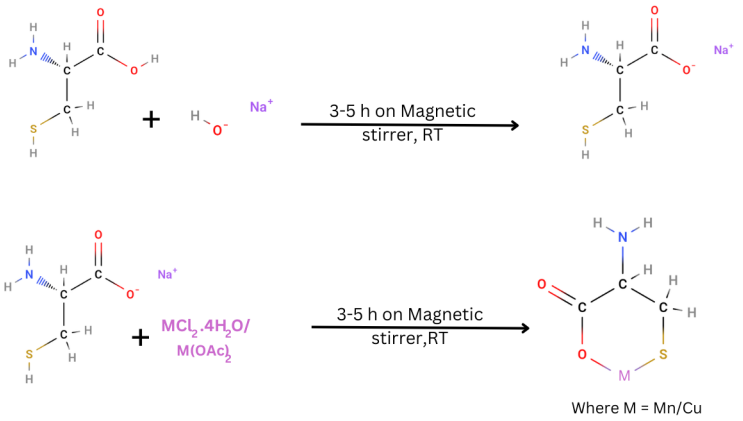

Scheme 1: Schematic depiction of Metal Complex creation of Mn (II) / Cu (II).

Yield,

$Mn[C_3H_5NO_2S]$, 68%.

$Cu[C_3H_5NO_2S]$, 73%.

Instrumentations

A Carlo-Erba microanalyzer was used to analyze the elements Carbon (C), Hydrogen (H), Nitrogen (N) and Sulphur (S). Metal contents estimated by standard procedure FTIR spectroscopy investigation was performed with 4000-400 cm^{-1} using Perkin Elmer equipment. UV-vis-NIR Spectroscopy was performed using a Perkin Elmer USA instrument Lambda 19.

The FT NMR Spectra were acquired

using a Bruker, Switzerland Advance III, Topsin 2.1 (400 MHz) using DMSO d6 as the solvent. The Metal CM-180 Eliodigital Conductivity meter was used to test conductance.

Biological Studies Biocidal Properties

The antimicrobial effects of the investigated compounds were tested *in vitro* against the bacterial species *Escherichia coli* (*E. coli*) and *Klbsiella Pneumoniae* (*K. Pneumoniae*) as well as the fungal species *Aspergillus niger* (*A. niger*) and *Candida albicans* (*C. albicans*). The Kirby Bauer Disk diffusion method was used by testing Chloramphenicol and nystatin were used as Standard antibacterial and antifungal agents. The tested Compounds were dissolved in a DMF Solution which did not exhibit any inhibition activity. The experiment involved placing a filler paper disk with a diameter of 5 mm and a thickness of 1 mm, soaked in a solution, onto a culture medium Bacterial species were cultured for 24 hr while Fungal Species were incubated for 72 hr, both at a temperature of 37°C. The Minimum Inhibitory Concentration (MIC) of the Compounds was measured using a serial dilution method.

Anticancer Studies

In addition, the produced metal Complexes were assessed for their anticancer activity against various human cancer cell lines using the MTT assay(3-(4,5-dimethylt hiazole-2-yl)-2,5- diphenyltetrazolium.

RESULTS

Selection of ligand

Metal Complexes containing a cysteine ligand are currently being studied for their biological properties, such as their ability to kill microorganisms and their potential as anticancer agents. To prepare these complexes a specific amount of sodium salt of cysteine ligand was added to a solution of manganese chloride/ Copper acetate in methanol. The mixture was stirred on a magnetic stirrer for 3-4 hr at room temperature. The resulting-coloured product was then filtered, washed with ethanol followed by ether and dried finally. The product was characterized using Elemental analysis, molar conductance measurements and spectroscopic studies.

Characterization of ligand and its metal complexes

The results of elemental analysis (C,H,N,M) melting point/ decomposition temperature and molar conductance of compounds are presented in Table 1.

IR Spectral Studies

The ligand's infrared spectra displayed prominent characteristics. The peaks at 3527 is attributed to the Stretching of the NH band in a protonated amine. The COO^- group exhibited asymmetric and symmetric vibrations at 1576 cm^{-1} and 1380 cm^{-1} respectively. These peaks correspond to the frequencies of amino twisting, rocking and carboxylate wagging which were reported within the range of 1296-607 cm^{-1}. A Strong absorption band was found at 2097 cm^{-1} which was ascribed to the stretching mode of the SH group. The observed downward charge in the vibration frequency (C-S) of Metal complexes suggests that the ligand is coordinating

with the metal ions via the Sulphur atom. The Stretching frequencies of the M-S band in the Complexes were observed at 450 cm^{-1} and 498cm^{-1}, providing evidence of the interaction between the Sulphur atom and the Cu (II) and Mn (II) metal ions. The presence of bands at 844 cm^{-1} and 871 cm^{-1} in metal complexes signifies the occurrence of C-S Stretching Vibration in the solid state and M-O bands appeared at 500-538 cm^{-1} in metal complexes. Because after NaOH was added in an equimolar amount during formation of ligand S-H frequency disappeared but the C-S and M-O vibration appeared in the metal complexes. The absorption frequency band at 1656 cm^{-1} was ascribed to the C=O stretching vibration in the spectrum of the ligand and it was shifted to 1575 cm^{-1} and 1576 cm^{-1} in the metal complexes which is an indication of the involvement of this group in metal ligand band formation. As the metal oxygeninteraction strengthens, the COOH group becomes increasingly asymmetrical (Stipanuk, 1986; Irfandi *et al*., 2023; Cormier *et al*., 1974; Dharmaraja *et al*., 2013).

Electronic Spectral Studies

The assignments have been completed using established sources and previous research conducted by many authors. The absorption bands within the range of 200 to 400 nm in Both the complexes of Cu (II) and Mn (II) ions were ascribed to the organic component, whereas the absorption peaks above 400 nm were ascribed to the establishment of the metal-ligand link. The n-π* characteristic band attributed to the C=O band was observed at wavelength

ranging from 250 to 370 nm in the metal Complexes. In the ligand Spectra this band occurred at wavelength between 270-290 nm which further confirmed the participation of the carboxylate ion in the formation of complexes exhibited bands associated with π-π* transition which were observed within the wavelength range of 270-390 nm. In contrast the free ligand displayed these bands at a narrower range of 270-280 nm. The absorption band observed 269- 378 nm in the complexes can be attributed to the n-σ* transition which was previously detected at 269-278 nm in the free ligands. The Complexes exhibited the presence of π-π*, n- π* and n-σ* bands indicating the presence of the functional groups (C=O and NH_2) from the Parent ligand. The Cu (II) and Mn (II) metal complexes exhibited a significant displacement of the absorption band, resulting in the emergence of a new band for d-d electronic transition. This suggests that Complexes have the potential to create metal ligand coordination bands. Transition metal complexes typically exhibit coloration which is attributed to the absorption of light within the visible spectrum. Hence, the bands detected above 400 nm in all the compounds are attributed to the d-d electronic transition (Krimm, 1976; Seema *et al*., 2024; Shyni *et al*., 2024; Balasubramanian *et al*., 2006; Denning, 1989).

Nmr Spectral Studies

^{1}H-NMR Spectra

The signals observed at 2.80 ppm and 3.10 ppm in the free ligand were identified as CH(α) and CH_2(β) protons respectively. In the ^{1}H-NMR Spectra of all the synthesized complexes, a signal was observed at 2.79 ppm, indicating coordination with ligand. Additionally, there was a significant downfield shift (4.6-4.7 ppm) of the NH_2 proton compared to its value of 6.1 ppm in corresponding amino acid in the zwitterionic form. It has been proposed that ligand forms complexes with Cu (II) and Mn (II) by binding to their amino groups. In the ^{1}H-NMR Spectra of all produced complexes, a downfield shift was seen at 6.69 ppm due to the NH_2 and NH protons (Tugarinov *et al*., 2002; Pretsch *et al*., 2000).

The Spectra of the metal Complexes, a signal of 3.3 ppm was observed for the methyl protons which appeared at 2.92 ppm in free ligand. Additionally, the signal for the ligand's imine protons shifted from 7.15 ppm to a range of 9.18-9.30 ppm in the metal Complexes Spectra indicating coordination through N_2 and N_4 atoms (Fabretti *et al*., 1984; Betts *et al*., 2020).

^{13}C –NMR Spectra

In ^{13}C-NMR Spectra resonance of CH(α) and CH_2(β) in L-Cysteine were observed to shift to higher values in the mixedligand Complexes. This shift was compared to the resonances in the free ligand which were measured at 56.50 and 26.12 ppm for CH_2(α) and CH(β) respectively. These results confirm that the thiol sulfur and amino nitrogen atoms are involved in coordinatively

Table 1: Physical and analytical data of Compounds.

Comp No.	Compound	Colour		% analysis (found)/calc				MP (°C)/ DT	Molar conductance ($Ohm^{-1}m^2 mol^{-1}$)
			C	H	N	S	M		
1	$C_3H_6NO_2SNa$	White	(24.23) 26.86	(3.62) 4.47	(8.79) 10.44	(21.20) 23.88	-	285	-
2	$Mn[C_3H_5NO_2S]$	White	(19.2) 20.6	(1.76) 2.87	(7.80) 8.04	(17.72) 18.39	(29.92) 31.60	290	7.42
3	$Cu[C_3H_5NO_2S]$	Blue	(18.58) 19.72	(2.0) 2.73	(6.83) 7.67	(16.84) 17.53	(33.59) 34.79	260	6.90

Table 2: Biochemical Studies (MIC µg/mL) data.

Compound number		Bacterial Species		Fungal Species	
		E. coli	*K. pneumoniae*	*A. niger*	*C. albicans*
1	$C_3H_6NO_2SNa$	30	35	40	38
2	$Mn[C_3H_5NO_2S]$	25	27	23	28
3	$Cu[C_3H_5NO_2S]$	20	22	25	27
4	Chloramphenicol	14	12	-	-
5	Nystatin	-	-	10	12

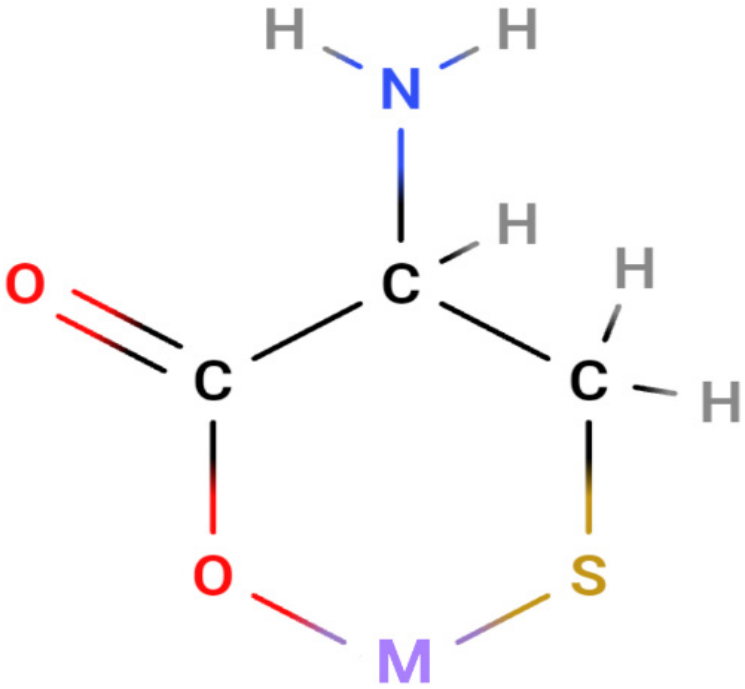

Figure 1: Proposed Structure of Synthesized Metal Complex where M = Cu (II) / Mn (II).

with the metal ions, as previously reported in references (Tobias and Hemminger, 2008). The signal owing to cysteine COO group did not experience considerable chemical shift because it is not involved in coordinating with the metal ions Cu (II) and Mn (II). The signals of imine carbon atoms were moved downfield by (157.18, 157.41 ppm) for all mixed complexes towards the corresponding signals. The primary carbon atom peaks were observed at (38.49-40.80 ppm) in all mixed complexes spectra which corresponds to the peak observed at (37.42 ppm) in the free ligand.

On the basis of spectral studies, the proposed structure of metal complex is shown in Figures 1 and 2.

Biocidal Studies

The free ligand and metal complexes were evaluated against bacterial and fungal species. The results are given in Table 2. In Figures 3 and 4 It has been reported that the Biocidal activity of Mn (II) and Cu (II) complexes are influenced by its stabilities. The lower stability of the amino acid complexes the greater is the Biocidal activity. This is probably because they have more free ions in the solution, which can enhance the cooperative interaction between the metal ions and the ligands. Metal Complexes of Mn (II) and Cu (II) were found more active as compared to ligand fragments. (Marras and Daley ; 2002; Karpin *et al* ; 2013). The reason is based on the fact that the Biocidal activity in the Chelated complexes, the positive charge of the metal is partially atoms present in the cysteine ligand and there is π electron delocalization over the whole chelate ring. This in turn increases the lipophobic character of metal complexes and favours its permeation through the lipid layers of microbial membrane. There are other factors which also increase the Biocidal activity of metal complexes as compared to cysteine ligand such are solubility, conductivity and bond length between the metal and the ligand which may explain the values resisted in the present case (Farhangian and Kharat ; 2023; Maisuria *et al*; 2011).

Table 3: Half maximum inhibitory concentration of synthesized metal complexes IC_{50} Values expressed in µM.

Compound no.	Compound	BT474	HOP62
2	$Mn[C_3H_5NO_2S]$	2.46	3.70
3	$Cu[C_3H_5NO_2S]$	2.80	4.10
6	Doxorubcin	1.69	1.14

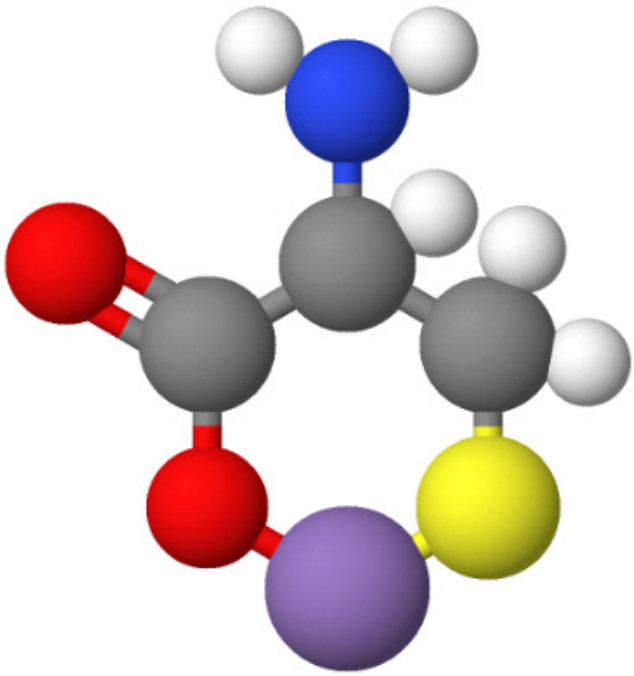

Figure 2: Ball & Stick representation of Metal complex.

Anticancer Studies

The produced metal complexes of Mn (II) and Cu (II) ions were initially screened to determine the potential as anticancer agents. This screening involved testing the complexes against a specific group of human cancer cell lines including BT 474 and HOP 62 using the MTT assay. The IC_{50} values obtained from cytotoxic testing are given in Table 3. Doxorubicin was employed as a positive control. The observed antiproliferation effect of the tested complexes is most likely attributed to their lipophilicity, which facilitates the transport of Mn (II) and Cu (II) complexes into the cell and subsequently into the organelles. Once inside the organelles these metals may potentially contribute to toxicity by inhibiting cellular respiration and the metabolism of biomolecules (Annuar *et al*., 2021; Yan *et al*., 2005; Zhang *et al*., 2007).

DISCUSSION

The Complexes were subjected to elemental analysis and metal estimation resulting in the formula $M[C_3H_5NO_2S]$ where M=Mn (II)/Cu (II). The experimental values closely align with theoretical values (provided in the parentheses). The low molar conductance values suggest that the complexes lack electrolytic properties. The ligand's IR Spectra exhibited distinct features. A prominent absorption band was detected at 2097 cm^{-1} which was attributed to the stretching mode of SH group. The decrease in vibration frequency (C-S) of metal complexes indicates that the ligand coordinates with the metal ions through Sulphur atom. The Complexes exhibited stretching frequencies of the M-S band at 450 cm^{-1} and 498 cm^{-1} indicating the interaction between the Sulphur atom and Cu (II) and Mn (II) ions. The n-π characteristic bond associated with the C=O bond is found in the metal complexes of Mn (II) and Cu (II) within a wavelength range of 250-270 nm. The ligand spectra of this band were found at a wavelength range of 270-290 nm providing further confirmation of the involvement of carboxylate ion in the formation of complexes. These complexes displayed bands associated with π-π transition which were observed within the wavelength range of270- 280 nm.

In the ^{1}HNMR spectra of the metal complexes, a signal was observed at 2.79 ppm, indicating coordination with the ligand. Additionally, there was a significant downfield shift (4.6-4.7 ppm) of the NH_2 proton compared to its value of 6.1 ppm in the corresponding amino acids in the zwitter ionic form. A hypothesis suggests that the ligand can create complexes with Cu (II) and Mn (II) ions by attaching to their amino acid groups. In the 1HNMR spectra of all formed compounds with Cu (II) and

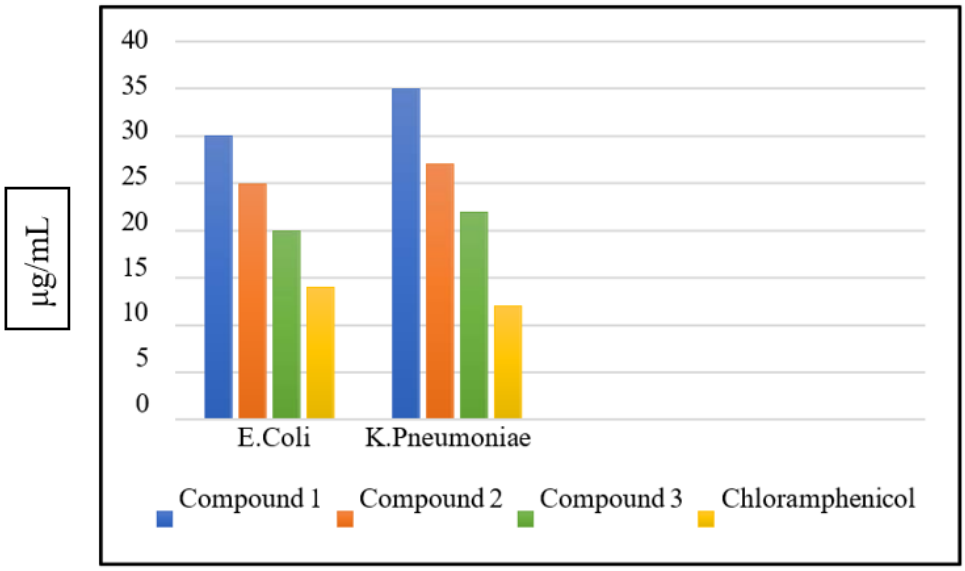

Figure 3: Antibacterial Studies of Ligand and its metal Complexes against *E.coli* and *K. pneumoniae*.

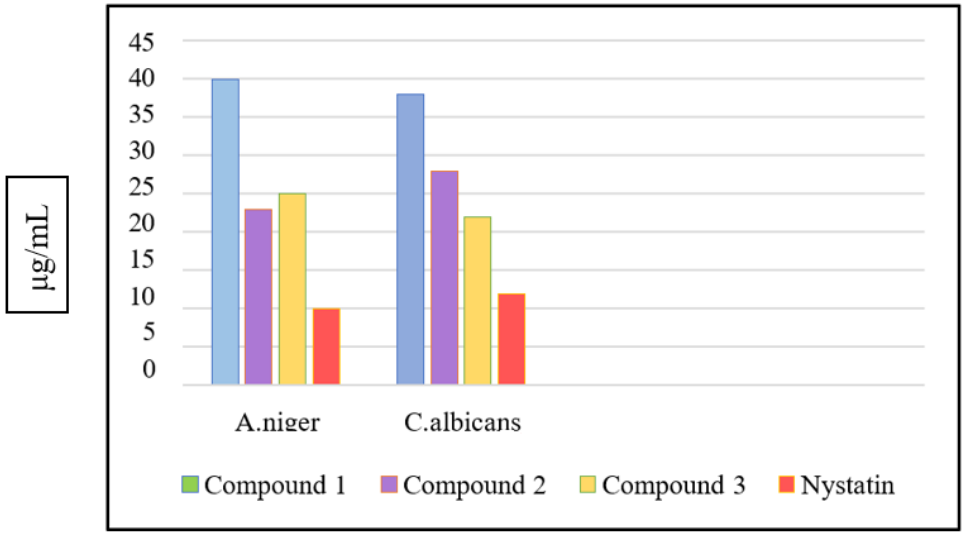

Figure 4: Antifungal studies of Ligand and its metal complexes against *A.niger* and *C. albicans*.

Mn (II) ions downfield shift was noted at 6.69 ppm due to the NH_2 and NH protons.

In ^{13}C-NMR spectra resonance of CH(α) and CH2(β) in cysteine ligand were observed to shift to higher values in the metal complexes. This shift was compared to the resonance in the free ligand which were measured at 56.50 and 26.12 ppm for CH_2(α) and CH(β) respectively. These results confirm that the thiol sulfur and amino nitrogen atoms are involved in coordinating with the metal ions.

Suggested structure of the Complex

The proposed structure of the complex is based on the above-mentioned physio-chemical, spectral studies like elemental, molar conductance, IR, Electronic, NMR. The tentative structure of the complex is shown in Figures 1 and 2.

The result of Biocidal studies of the ligand and its metal complexes of Cu (II) and Mn (II) Indicate that complexes show more activity as compared to ligand fragments. The results of anticancer studies show that the coordination of Ligand with metal ions Cu (II) and Mn (II) indicate that complexes show more activity as compared to ligand fragment. The results of anticancer studies show that coordination of ligand with metal ions Cu (II) and Mn (II) enhance the activity of the metal Complexes against BT 474 and HOP 62 cell lines.

CONCLUSION

Cysteine and its Mn (II) and Cu (II) Complexes were prepared and characterized using the microanalytical, conductance, and spectral analysis. The complexes are biologically active and showed enhanced Biocidal activity as compared to free ligand.

Synthesized metal complexes were also found to be effective in all the human cancer cell lines.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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ABBREVIATIONS

DMSO: Dimethyl Sulphoxide; **DMF:** Dimethyl Formamide; **IR:** Infrared Spectra; **UV:** Ultraviolet Spectra; **NMR:** Nuclear Magnetic Resonance; **PPM:** Parts Per Million; **MIC:** Minimum Inhibitory Concentration.

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