Original Article

Synthesis, Spectral Characterization and Pharmacological investigation of Zn(II) and Hg(II) complexes with biologically active N- donor ligand

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Abstract: *Fluconazole and benzoate ion ligand were used to synthesize new mononuclear Zn(II) and Hg(II) complexes one after the other. The created metal complexes were described using physical and spectroscopic methods (Elemental analysis, molar conductance, UV, IR spectra, etc.,). The results demonstrate that whereas the nitrogen of the imine group in the synthesized fluconazole served as a bidentate ligand and linked it to metal ions, the benzoate ion connected to metal ions through oxygen. The disc diffusion method was used to evaluate the antimicrobial properties of Candida albicans, Aspergillus flavus and Aspergillus Niger strains for fungus and Staphylococcus and Escherichia coli, strains for bacteria. By observing how the complexes and the ligand interact with the stable free radical DPPH, their free radical scavenging abilities have been quantified. Compared to ligands, complexes exhibit greater antioxidant action.*

Keywords: *Diamagnetic, Fluconazole, Benzoate Ion,Antioxidant.*

INTRODUCTION

Throughout the world, invasive fungal strains pose a severe threat to human health, agriculture, and the environment. Aspergillus, Candida, Cryptococcus, and Pneumocystis species are the most common causes of the 1.5 to 2 million fatal fungal infections each year, according to [1,2]. Patients with weakened immune systems, such as those who have received solid organ transplants or hematopoietic stem cell therapy, and those who have HIV infection are particularly vulnerable to these pathogens, according to [3-5]. Four kinds of organic compounds, categorised by their mechanisms of action, are now used to treat fungus infections. Amphotericin B and nystatin are polyenes; caspofungin and micafungin are azoles; micafungin is an echinocandin; and 5-fluorocytosine [6] is an antimetabolite.

Azoles are the most widely used antifungal agents [7] due to their broad-spectrum antifungal action, excellent effectiveness, and acceptable safety profile. This class of antifungal substances inhibits the enzymes (cytochrome P450) involved in the formation of ergosterol, a component of the fungal cell membrane [8-10]. As a triazole from the first generation of azoles, fluconazole (fcz) was traditionally used to treat infections brought on by Candida species like C. albicans, C. tropicalis, C. parapsilosis, and dermatophytes. Due to fluconazole's limited antifungal spectrum, development of resistance, and other drawbacks, it is urgent to discover novel compounds that can address these issues.

Fluconazole and benzoate have been used as ligands to create metal complexes of Zn(II) and Hg(II) that have been spectrally analyzed. Research in pharmacologicalalso focuses on ligands and their complexes..

EXPERIMENTAL METHOD

Materials:

The Alfa Aaser Company provided the sodium benzoate, metal nitrate, and fluconazole (Flz), which were used as such. The used organic solvents, DMSO, DMF, methanol, and ethanol of AnalaR-grade, were used directly without additional purification.

Synthesis Of Zn(II) Complex With Fluconazole:

The methanolic solution of nickel nitrate (1.00g (3.23 mmol) was added to 1g (3.31 mmol) of fluconazole in MeOH and 0.61g (6.39 mmol) of sodium benzoate in EtOH, and the combination was then microwave-irradiated for a few minutes after each addition. The precipitate was filtered out, washed with a 1:1 methanol:ethanol solution, and vacuum-dried after removal. A colorless complex was created with a yield of 45.24%.

Synthesis Of Hg(II) Complex With Fluconazole:

1.14g (3.67 mmol) of fluconazole and 0.77g (7.59mmol) of sodium benzoate were both present in the mercury nitrate 1.11g (3.87 mmol) methanolic solution. The mixture was irradiated for a short while using microwave oven after each addition. Filtration was used to extract the precipitate, which was then washed with a 1:1 methanol: ethanol solution and dried by hoover. It was possible to create a colorless complex with a yield of 44.12%.

Instrumentations:

The elemental analysis of C, H, and N was performed using a Thermo Finnegan Flash EA1112 CHNS(O) analyzer. The Systronic Conductivity Bridge (model 304) was used to evaluate the molar conductivity of metal complex solutions in acetonitrile at 10–3 M concentrations. On a UV-Vis spectrophotometer with the Varian Cary 5000 model, the conjugates' UV-Vis spectra were captured. Using a Perkin Elmer Spectrum RX-I FT-IR spectrometer, conjugates and ligands' infrared spectra were captured on KBr discs while they were at room temperature. Using a JES FA 200 EPR spectrometer, the electron paramagnetic resonance spectra of copper complexes were measured at room temperature.

Antimicrobial activity:

The well diffusion method was used to investigate the in vitro antibacterial activity of the free ligands and their complexes utilizing the agar nutrient as the medium. The well diffusion method was used to assess the ligands' antibacterial and antifungal properties against strains that had been cultivated on potato dextrose agar as a substrate. A well was created on the agar medium that had been injected with the microorganisms in this normal technique [11,12]. A micropipette was used to add the test solution to the well, and the plate was incubated at 35 °C for 24 hours for bacteria and 72 hours for fungus. The inhibitory zones that had developed on the medium at the end of the time were measured in millimetres (mm).

Antioxidant Activity:

Antioxidant testing DPPH (1,1-diphenyl-2-picryl-hydrazyl) was created as a set assay for in vitro radical scavenging evaluation [13] because it exhibits immediate and constant activity for the examined substances. Ascorbic acid (Vitamin C) was used as the standard medication, and the DPPH radical scavenging activity was determined by measuring the change in DPPH's molar absorbance value at 517 nm at various doses (100, 200, 300, 400, and 500 g/mL) in DMSO[14]. One mL of the aforementioned solutions should be added to one mL of DPPH solution (5 mg per 100 mL) produced in DMSO. The volume of the resulting solution should then be increased with more DMSO. The prepared mixture was shaken briskly and kept at room temperature for about 30 minutes in complete darkness. DPPH and DMSO were used as a reference or blank to determine the compounds' molar absorbance at 517 nm. The colour change of the solution and the DPPH values at 517 nm, which both help measure the antioxidant's radical-scavenging ability, are proof that the antioxidant is actively scavenging DPPH radicals by donating a hydrogen radical or electron to create a stable DPPH-H molecule. The proportion of DPPH's free radical generation that was prevented by radical scavenging activity was calculated using the formula below:

$$\frac{Abscontrol - Abssampl}{Abscontrol} \times 100$$

Where $Abs_{control}$ stands for the absorbance of the blank and Abs_{sample} for the absorbance of the sample. Each test experiment was carried out in triplicate, the data were averaged, and the mean and standard deviation were calculated. A graph is drawn between the concentration (g/mL) on the X-axis and the % scavenging effect on the Y-axis[15,16].

RESULTS AND DISCUSSION

Elemental analysis:

The molecular formulas for the metal complexes were derived from the elemental analytical data. It matched the theoretical values perfectly. Based on each complex's molecular formula[17] (Table 1), the theoretical values in parentheses are calculated.

**Table 1. Analytical and physical data of the ligands and their complexes**

| Compound	Mol. Formula	Mol. Weight	Color	Carbon, %		Hydrogen, %		Nitrogen, %		Oxygen, %	
				Expt	Calcd	Expt	Calcd	Expt	Calcd	Expt	Calcd
Fluconazole	$C_{13}H_{12}F_2N_6O$	306.277	White	55.15	55.17	3.92	3.91	29.41	29.38	54.89	55.22
Sodium benzoate	$C_7H_5NaO_2$	144.11	White	62.15	63.19	3.44	3.47	-	-	21.81	22.13
[Zn(Flz)(Ben)$_2$]	[Zn($C_{13}H_{12}F_2N_6O$)($C_7H_5O_2$)$_2$]	548.49	Color less	41.03	42.35	3.23	3.58	12.91	13.7	13.37	13.03
[Hg(Flz)(Ben)$_2$]	[Cd($C_{13}H_{12}F_2N_6O$)($C_7H_5O_2$)$_2$]	748.47	Color less	35.11	34.79	3.01	2.93	11.02	11.21	10.01	10.68

Molar conductance:

At a concentration of 10^{-3}M, molar conductance measurements on the complex using acetonitrile as the solvent showed that the complexes did not act like electrolytes [18,19]. Complexes of the type 1:0 non-electrolyte nature can be created.

Electronic spectrum of complexes:

Since the zinc ion has a d^{10} structure, a charge transfer transition could be the cause of the absorption at 270 nm. However, a tetrahedral geometry [20] might be predicted for its complex based on the spectra and configuration of the zinc(II) ion. In the same way mercury ion has a d^{10} structure as well, and its absorption at 320 nm might be attributed to a charge transfer transition [21] and its complex could be believed to have tetrahedral geometry.
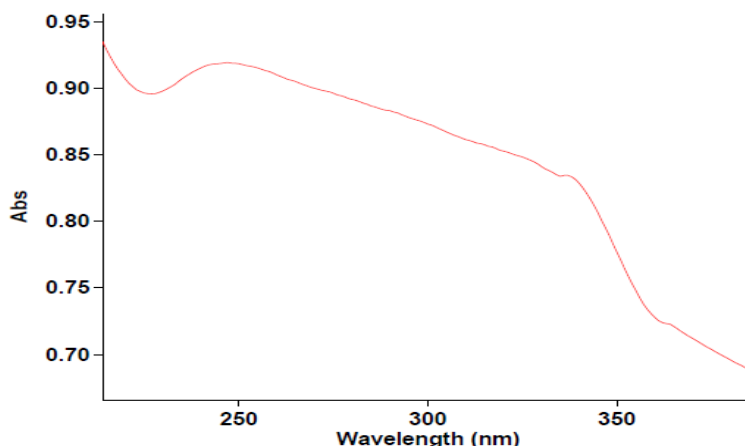
Fig.1 Electronic spectrum of Zn(II) complex
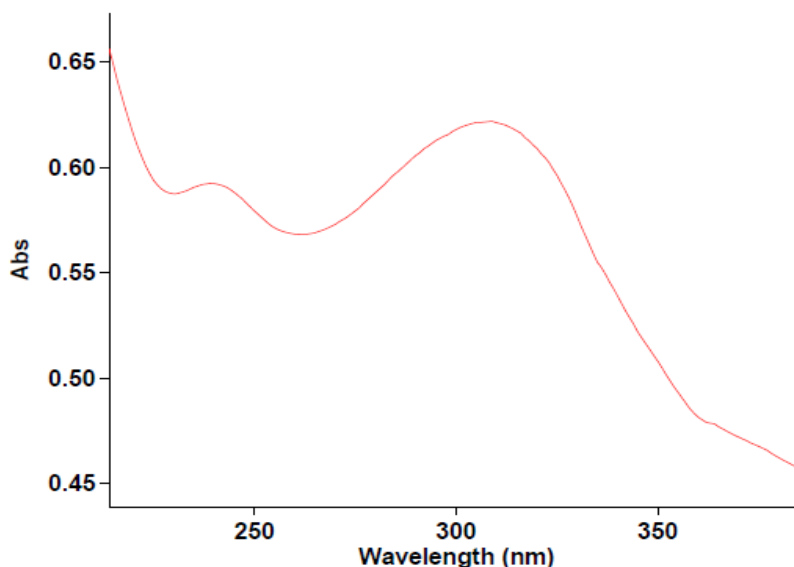
Fig.2 Electronic spectrum of Hg(II) complex

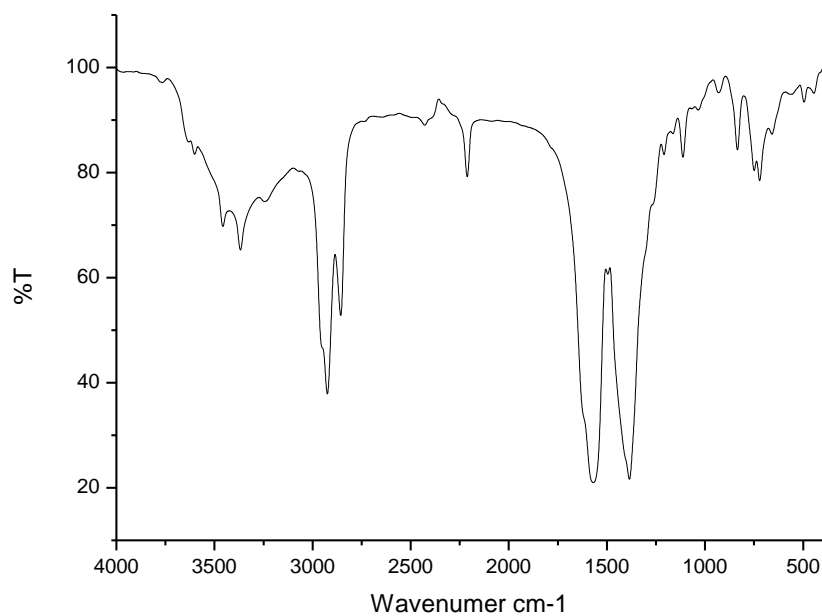**FT-IR Spectra of free ligands and their complexes:**

The region between 4000 and 400 cm-1 was used to record the FT-IR spectra of the free ligands and their complexes [22]. Strong and mild absorption bands at 1612 cm-1 and 1597 cm-1, respectively, are present in the fluconazole (Flz) FT-IR spectrum, according to C=N stretching vibrations [23,24]. The stretching vibrations showed separate peaks at 3298 cm-1 (OH stretch), 1580 cm-1 (C=C aromatic symmetric stretch), and 1512 cm-1 (C=C aromatic asymmetric stretch) at 1107 cm-1 weakly and significantly. The bands at 1612cm-1 and 1597 cm-1 that were lowered to lower frequencies showed that fluconazole was coordinated to metals in a bidentate manner through the imine nitrogen of C=N in metal complexes [25,26].Additionally, the IR spectra of the organised complexes were compared to those reported for the benzoate ion complexes. The M-O coordination is confirmed by the benzoate ion COO- stretching frequency, which increased to nearly 1215cm-1.
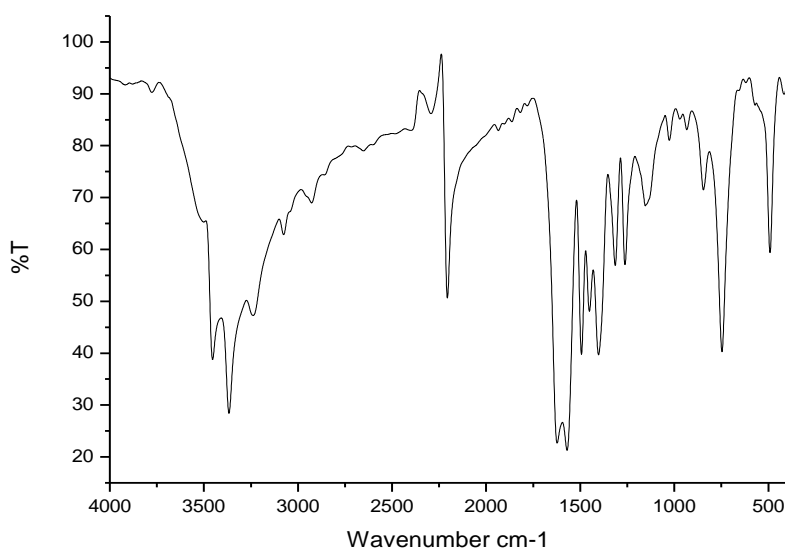
Fig.3 FT-IR spectrum of fluconazole
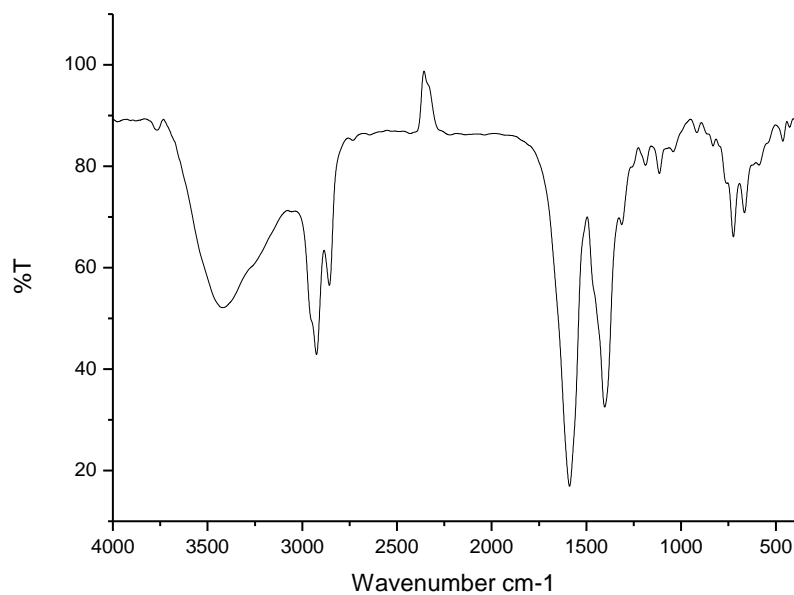
Fig.4 FT-IR spectrum of fluconazole

Fig.5 FT-IR spectrum of Zn(II) complex
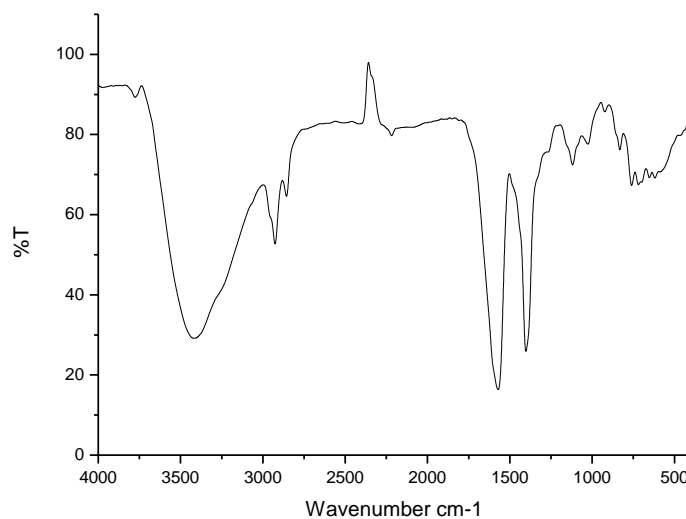
Fig.6 FT-IR spectrum of Hg(II) complex
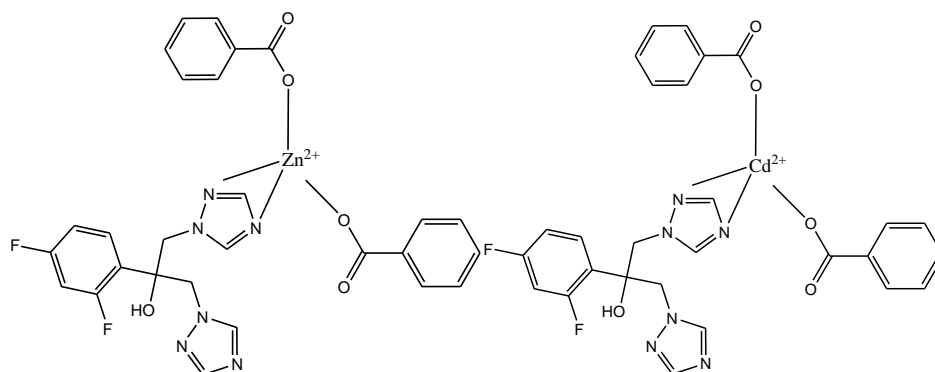
Structure of the prepared complexes

BIOLOGICAL ACTIVITY

Antibacterial Activity:

The synthesized complexes and the free ligand fluconazole are tested against the bacteria *viz.*, *Staphylococcus* and *Escherichia coli* by agar-well diffusion method in *vitro* conditions. The complexes haveprospective activity against thebacteria compared to free ligand(Fig.7).

| Fluconazole | Zn(II) complex | Hg(II) complex | Hg(II) complex |
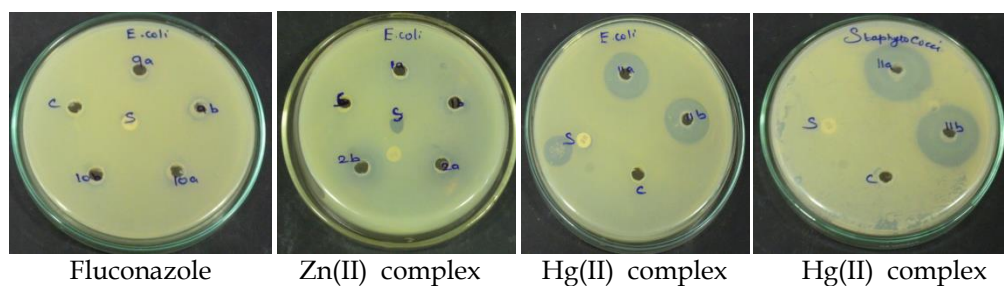
Fig.7 Antibacterial activity of ligand and its complex

Antifungal activity:

The antifungal activity of the free ligand Flzand the synthesized complexes are tested against the fungi *viz.*, *Candida albicans, Aspergillus flavus* and *Aspergillus Niger*by agar -well diffusion method. The complexes haveenhanced activity against thefewfungi compared to free ligand (Fig.8).
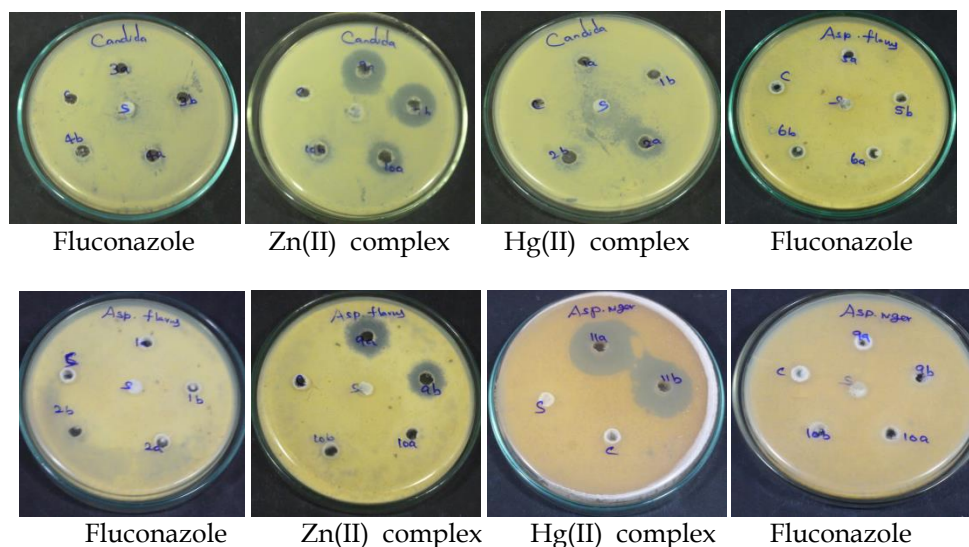

| Fluconazole | Zn(II) complex | Hg(II) complex | Fluconazole |

| Fluconazole | Zn(II) complex | Hg(II) complex | Fluconazole |

Fig.8 Antifungal activity of ligand and its complex

Antioxidant activity (Radical Scavenging Activity):

Scavenging activity of the freelig and fluconazole and the complexes were determined using the DPPH scaven germethodand vitamin Casastandard. Thereducingability of DPP Hradicals was determined by the antioxidant-induced decrease in absorbanceat 517nm [32].The graphplots percentage capture efficiency on they-axis and concentration (ug/ml)onthex-axis. Thes cavenging capacities of complexes were compared with vitamin Casastandard [33-41].Metal complexes showed enhanced activity asradical scaven gerscompared to ascorbicacid. These results arein good agreement with previous metal complex studies where theligan disexpected to havean tioxidan tactivity and them etalmoi etyenhances tha tactivity [42-46].Thes cavenging activity ofligands and their complexesis showninFig.9.

Table 2 Antioxidant activity ligand and its complexes

| S.No	CONCNµg/ml	Zn(II) complex	Hg(II) complex	Fluconazole	Benzoate	Vitamin C
1	500	57.531	40.33	16.491	11.066	90.22
2	250	49.302	32.982	11.387	9.79	92.03
3	125	38.617	25.742	9.57	6.382	93.22
4	62.5	29.088	16.198	7.462	5.177	93.09
5	31.25	21.136	11.54	6.091	4.469	88.92
6	15.625	16.728	9.725	4.579	3.912	75.23
7	7.8125	13.94	7.013	3.12	3.168	38.72
8	3.90625	11.351	6.785	2.398	2.22	25.68
9	1.953125	11.179	6.381	1.936	1.681	11.99
10	0.976563	11.004	6.054	1.61	1.492	
IC 50		**291.268**	**578.46**	**>1000**	**>1000**	
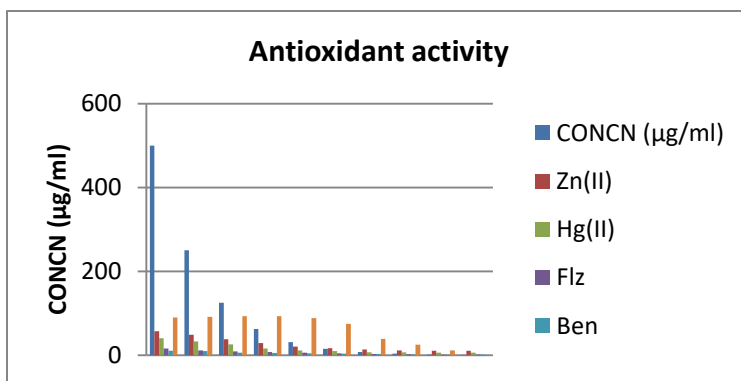
Fig. 9 Antioxidant activity of ligand and its complexes

CONCLUSION

In this study, our efforts was to synthesize and characterize a metal complexes Zn(II) and Hg(II) complexes with fluconazole and benzoate ion as ligands. The new complexes were synthesized using microwave irradiation. The synthesized complexes were characterized by various chemical and spectral analyses. The synthesized complex was tested for antimicrobial activities. The metal complex has significant antimicrobial and antioxidant activities as compared to the free ligands.

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Conflict of Interest:

I hereby declare that all the authors and corresponding authors do not have any conflict of interest.

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