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SYNTHESIS, CHARACTERIZATION, ANTIOXIDANT, LARVICIDAL, DNA-CLEAVAGE AND IN-VITRO ANTITUMOUR ACTIVITIES OF SOME NOVEL SCHIFF BASE TRANSITION METAL COMPLEXES DERIVED FROM CURCUMIN AND SEMICARBAZIDE

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ABSTRACT

In this paper, a new Schiff base ligand (L), was prepared by condensation of 1, 7-bis-(4-hydroxy3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione (Curcumin) with Semicarbazide. The transition metal complexes of Ligand, (M= Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) were also successfully synthesized and characterized by various spectroscopic techniques. The ligand and their complexes were characterized by powder XRD and SEM-EDAX analysis. All the synthesized compounds were screened for their anticancer activities against breast cancer cell line MCF-7 and Leukemia cancer cell line K562 by sulforhodamine-B (SRB) assay. Interestingly, the Schiff base (L) and its Mn (II), Co (II) and Zn (II) metal complexes showed superactive anticancer activity against MCF-7 and K562 cell lines. The DNA cleavage experiment performed using agarose gel electrophoresis method showed the cleavage of DNA by all metal complexes. In addition, the antioxidant and larvicidal activities were also done for all the metal complexes. The percentage of antioxidant scavenging activity and mortality of the larvicidal activity were also determined.

KEYWORDS

Curcumin, Transition metal complexes, XRD, SEM-EDAX, Antioxidant and Larvicidal activities.

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INTRODUCTON

Coordination chemistry, comprise a large body of current inorganic research. Schiff bases are widely used as ligands in coordination chemistry[1]. Schiff bases are prepared by the condensation of aldehydes or ketones with primary amines. Schiff bases are used as ligands in the preparation of transition metal complexes because of their preparative accessibility, solubility in common solvents, stereo chemical and electronic properties. Further, Schiff

base transition metal complexes exhibits promising applications like biological activity and biological modelling[2-3]. 1, 7-bis-(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione (Curcumin), one of the most effective constituent of the everyday using turmeric commonly known as Indian spice scientifically termed as curcuma longa[4]. Curcumin exhibits protective effects against oxidative damage and is a potent cancer chemo preventive agent[5-6]. Recently, it has been considered as a key molecule for development of novel therapeutics for Alzheimer's disease[7]. Curcumin derived metal complexes possess anticancer, antimicrobial/antifungal activity, antiarthritic, antiviral, anti-HIV, biological imaging/ radioimaging and DNA intercalating properties[8]. Semicarbazides are compounds have adaptable features and can coordinate either as neutral ligand or deprotonated ion to metal. Semicarbazones molecules also hold great importance due to their pharmacological properties such as antibacterial, antifungal, antihypertensive, hypolipidemic, antineoplastic, hypnotic and anticonvulsant[9-10]. Ketones and aldehydes due to their additional donor atoms enhances the coordination possibilities in semicarbazones[11-12]. Based on the above facts the prime aim of the present work was to synthesize a series of Schiff base transition metal complexes derived from Curcumin and Semicarbazide, evaluate the Antitumour activity and DNA cleavage activity of the synthesized metal complexes. Also, the synthesized metal complexes were screened for larvicidal and *invitro* antioxidant activity.

MATERIAL AND METHODS

All the chemicals and solvents used in the preparation of ligands and their metal complexes were of A.R grade. Curcumin and Semicarbazide were purchased from Sigma-Aldrich. Metal salts like Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) chlorides and the solvents were purchased from Merck.

Synthesis of Schiff base ligand 2-[5-hydroxy-1, 7-bis (4-hydroxy-3-methoxyphenyl)-hepta-1, 4, 6-triene-3-ylidene] hydrazine carboxamide [L]

Curcumin (0.01 mol, 3.6839g) was dissolved in 20 ml methanol and stirred well at room temperature. Then methanolic solution of curcumin was added to a hot aqueous solution of semicarbazide and 0.02 g sodium acetate (0.01 mol, 0.7508g) was added to the prepared solution. The obtained orange coloured mixture was stirred and refluxed at 80^0C for about 6 hrs. After cooling, the resulting orange fine precipitate was filtered and washed well with distilled ethanol repeatedly to remove any unreacted chemicals. The obtained orange crystals were then dried at room temperature.

Synthesis of Schiff base metal complexes

To the hot solution of schiff base ligand (0.01 mol) in methanol (20ml) was added a hot methanolic solution (10ml) of respective metal chlorides (0.005 mol) drop by drop in 2:1 (ligand: metal) molar ratio. pH of the solution was maintained just below the value of hydrolysis of the metal ion using alcoholic ammonia. The reaction mixture was magnetically stirred and refluxed for 4 hrs at 80^0C. The coloured precipitate was filtered and washed by cold ethanol to remove the residue reactants. Finally the obtained powder was dried to get the complex.

Antioxidant assay (DPPH scavenging activity)

The antioxidant activity of the synthesized curcumin derivatives was evaluated using the DPPH (1, 1-Diphenyl-2-picryl-hydrazyl) free radical scavenging assay[13]. It is a rapid technique for screening the radical scavenging activity of specific compounds[14]. 100 g/ml of the test sample solution was added to 4ml of 0.01 M methanolic DPPH at various concentrations (20, 40, 60, 80 g). After stirring, the mixture was incubated for 20 min at room temperature and the absorbance at 517 nm was measured. Ascorbic acid (100 g/ml) was used as the standard. A blank was prepared without adding standard or test compound (95% methanol). Lower the absorbance of the reaction indicates higher the free radical scavenging activity. The capability to scavenge the DPPH radical were calculated using the equation,

$$\% \text{ of inhibition} = \frac{A_{control} - A_{sample}}{A_{control}} \times 100$$

Where $A_{control}$ is the absorbance of the control reaction and A_{sample} is the absorbance in the presence of test compounds[15].

***In vitro* analysis of Larvicidal activity**

The mosquito larvae were collected from water habitats of Nagercoil, Kanyakumari District using a wide mouth container. The mosquito samples were brought to the laboratory, morphologically identified using standard manual and used for larvicidal activity studies. Cleaned sterile Erlenmeyer flasks were taken and 10 early instar larvae of *Culex* were taken in 100mL of tap water. To that 100 ppm of synthesized complexes was added. The negative control was set up with sterile distilled water without metal complex while the positive control was the commercial larvicide with test solution. Percentage of mortality was assessed after 24 h of incubation. A number of dead larvae in each batch were counted every hour for 24 h exposure period. The treated larvae was mounted on a slide and examined under a microscope for image capture. The LC50 and LC90 of Cu (II) complex were determined in mosquito larvae (*Culex*). The mortality of the larvae was also tested by substituting 25, 50 and 100 ppm complex. It was incubated for 24 h and the percentage mortality was obtained[16].

DNA cleavage activity

In the present study, the DNA cleavage experiment was conducted using plasmid DNA by gel electrophoresis in the presence of H_2O_2 as an oxidant. The cleavage of supercoiled pUC18 DNA to its nicked circular form studied by using agarose gel electrophoresis. pUC18 DNA (0.3 µg) dissolved in 5 $mmolL^{-1}$ Tris-HCl/50 $mmolL^{-1}$ NaCl buffer (pH 7.2), was treated with the complexes. The mixture was incubated at 37 °C for 1 h and then mixed with the loading buffer containing 25% bromophenol blue, 0.25% xylene cyanol and 30 % glycerol. Each sample (10^{-3} M, 0.5 µL) was loaded into 1% (w/v) agarose gel. Electrophoresis was undertaken for 2h at 100 V in Tris-acetate-EDTA (TAE) buffer (pH 8.0). The gel was stained with ethidium bromide for 5 minutes after electrophoresis and then photographed under a UV transilluminator. To improve the DNA cleaving activity of the complexes, hydrogen peroxide (100µ$molL^{-1}$) was added to each sample.

Anticancer activity

The anticancer activity was performed at Tata Memorial Centre Advanced for Treatment, Research and Education in Cancer (ACTREC), Khar, Navi Mumbai – 410210, (MCF-7 and K562 cell line) by SRB assay. The principle behind SRB assay is, under acidic conditions, a bright pink aminoxanthine dye SRB binds dye to basic amino acid residues in TCA (Trichloro acetic acid) fixed cells to provide a sensitive index of cellular protein content that is linear over a cell density range of visible at least two order of magnitude. The cell lines were cultured in RPMI 1640 medium, supplemented with 10% fetal bovine serum (FBS) and 2 millimolar L- glutamine at 37^0C in a humidified atmosphere of 5% CO_2. About 5x103 cells/well were seeded in 96-well micro titer plate using a culture medium. After 24 hours, Schiff base (L) and its Mn(II), Co(II), Cu(II) and Zn(II) metal complexes at the concentrations of 10,20,40 and 80 µg/ml were added to respective wells at a single concentration and incubated for 48 hours. After incubation the sulforhodamine-B assay was performed[17-18].

The percentage growth inhibition was calculated using following formula,

% cell inhibition= 100-{(At-Ab)/ (Ar-Ab)} x100

Where, At = Absorbance value of test compound,
Ab = Absorbance value of blank,
Ar = Absorbance value of reference

RESULTS AND DISCUSSION

The condensation of Curcumin with Semicarbazide gives the Schiff base, 2-[5-hydroxy-1, 7-bis (4-hydroxy-3-methoxyphenyl)-hepta-1, 4, 6-triene-3-ylidene]hydrazine carboxamide [L]. The ligand which coordinated with Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} ions separately to give coloured complexes. The Schiff base ligand (L) and its metal complexes are stable at room temperature and soluble in almost all organic solvents like DMSO and DMF.

X-Ray Diffraction analysis

X-ray diffraction studies of Curcumin were investigated from the angle of 10^0 to 80^0. The powder XRD patterns of L and its Cu (II) complex are recorded in the range 2θ = 0-80 A^0 were shown in Figure No.1.

The average crystalline size d_{XRD} of the complexes was calculated using Scherrer's formula[19],

$$d = 0.89\lambda/\beta\cos\theta),$$

Where'd' is the average crystalline size of the phase under investigation. 'λ' is the wavelength of X-ray beam used. 'β' is the full width at half maximum of diffraction and 'θ' is the Bragg's angle. From the observed XRD patterns, the average crystalline size for the ligand, L and Cu (II) complex are found to be 86.77nm and 77.48nm respectively. After complexetion, the particle size decreases. This suggests that the ligand and the complexes are nanocrystalline in nature.

SEM – EDAX Analysis

Morphology of synthesized ligand and complexes were characterized by SEM analysis. SEM images of ligand L and its Cu (II) complex were shown in Figure No.2. SEM picture of the metal complexes shows that the particles are agglomerated with controlled morphological structure and the presence of small grains in non-uniform size. After agglomeration, SEM image of compounds shows irregular shaped grains with elongated morphology and increased particle size. The results of Energy Dispersive X-ray analysis (EDAX) data reveals the purity of the complex which indicates that there is no elemental contamination present in the complex. The EDAX result of ligand showed that the atomic percentage of carbon, oxygen and nitrogen are 75.04, 17.41 and 7.55% respectively whereas the % content of elements in the Cu (II) complex is C (57.02), O (22.60), N(9.70) and Cu (6.53) respectively.

Antioxidant activity

Antioxidant activity evaluation of ligand and its complexes was measured in terms of decreases in absorbance at 517 nm of DPPH methanolic solution (0.1mmol) produced by the effect of each compound as a result of their ability to donate a hydrogen giving to the reduced form of DPPH radical. The reducing abilities of the synthesized compounds were determined by their interaction with the free radical DPPH at 20 mg concentrations for 15 min. This investigation indicates that there is a greatest possibility of finding potent antioxidants. The antioxidant activity of ligand and metal complexes are given in Table No.1. The ligand (L) and its Zn (II), Ni(II), Co(II) and Mn(II) complexs have exhibited very good free radical scavenging activity. The Cu(II) complex, L-Cu were shown moderate activity. Zn (II) complex shows excellent free radical scavenging activity when compared to its ligand. The bar graph representation of percentage of free radical scavenging activity is shown in Figure No.4.

Larvicidal activity

The larvicidal activity of the Schiff base ligand and the copper complex was performed against the larvae of culex and the result of mortality values are listed in Table No.2. The *Culex* mosquito larva mortality was calculated of various concentrations of copper complexes in the range of 25 to 100ppm. Among the tested concentration, larva mortality was recorded from 25 to 100ppm concentration for the period of 60h, whereas the percentage of mortality was significantly increased from the 25 to 100ppm. The Cu (II) complex showed highly significant larvicidal activity than the ligand. Thus the larvicidal effect of these synthesized complexes may make these compounds to serve as potential insecticidal substances in mosquito control.

The average larval mortality data were subjected to statistical analysis for calculating LC_{50} and LC_{90} for synthesized Cu (II) complex. Minimum lethal concentration of the complexes indicates the more toxicity of the complex towards larvae.

LC50 value of copper complex = 35 ppm

LC90 value of copper complex = 60ppm.

The metal complex showed enhanced larvicidal activity than the Schiff base. The increased mortality rate observed for cu complex can be attributed to the increase in lipophilicity on complexation[20]. Chelation increases the lipophilic nature of the central metal atom, which in turn, favours the molecules in crossing the cell

membrane of the microorganism and enhancing larvicidal activity of complex.

DNA cleavage of Ligand and its metal complexes

In the present study, the DNA cleavage experiment was conducted using plasmid DNA by gel electrophoresis in the presence of H_2O_2 as an oxidant. The results of the first series of the ligand, L and its metal complexes are shown in Figure No.5. From the observed results of the ligand, L and its metal complexes, it is found that L-Co complex [lane 6], completely cleaved the DNA of bacillus into fragments. The complexes, L-Zn, L-Ni and L-Mn [lane 3, 5 and 7] showed enhancement activity whereas ligand, L [lane 2] and L-Cu complex [lane 4] doesn't show any cleavage activity. The result indicates the important role of coordination of nitrogen and oxygen to the metal in these isolated DNA cleavage reactions. It can be concluded that all the compounds under present study inhibited the growth of pathogenic organisms by DNA cleavage as has been observed on the DNA cleavage of supercoiled plasmid DNA pUC 18.

Lane 1 – DNA control,
Lane 2 – DNA + L + H_2O_2
Lane 3 – DNA + [L-Zn] + H_2O_2
Lane 4 – DNA + [L-Cu] + H_2O_2
Lane 5 – DNA + [L-Ni] + H_2O_2
Lane 6 – DNA + [L-Co] + H_2O_2
Lane 7 – DNA + [L-Mn] + H_2O_2

Evaluation of Anti-tumour activity

The *in-vitro* anticancer activity of the ligand (L) and its Zn(II), Cu(II), Co(II) and Mn(II) complexes was determined by sulforhodamine -B assay using ADR (Adriamycin) taken as a reference on human breast cancer cell line MCF-7 and human Leukemia cell line K-562. The test compounds were examined at various concentrations and the LC50, TGI and GI50 values obtained for each compounds are summarized in Table No.3. The good results however were obtained for all the complexes. Interestingly, all compounds were found to be active against Breast cancer cell line MCF-7. At the concentration of 10 mg/ml compounds L-Co, L-Zn and Ligand, L showed 17.6, 22.5 and 22.6 inhibition whereas for concentration 80 mg/ml, these compounds showed 21.9, 36.2 and 21.1 inhibition respectively, in compared to Adriamycin 20.3 and 2.8 inhibition indicating that these compounds possess anticancer activity to a greater extent.

Biological evaluation of Leukemia cancer cell line K-562 shows that, at the concentration of 10 mg/ml compounds L-Mn, L-Zn and ligand, L shows excellent anticancer activity. No activity was found for L-Cu and L-Co complexes. Among four dose level of compounds, maximum inhibitory activity was found at 80µg/ml. Percentage control growth results of all the compound are in line with reference ADR. Results shows that Ligand (L) and its Zn(II),Co(II) and Mn(II) complexes are super active on human cancer cell lines (MCF-7 and K-562) in the assay system used with GI_{50} near or less than 10 µg/ml which is comparable to that of Adriamycin (ADR), a standard positive control drug with GI_{50} value less than 10µg/ml. Therefore ligand and complexes may prove as lead compounds for in vivo screening of anticancer activity.

The morphological observation showed that cells had normal spindle shaped morphology at all (10, 20, 40 and 80 µg/ml) concentrations of various samples are shown in Figure No.6 and 7.

Table No.1: DPPH assay of L and its complexes

S.No	Compounds	% of Inhibition (mg/ml)
Control	-	100
1	L	97.9
2	L-Mn	97.7
3	L-Co	97.9
4	L-Ni	90.9
5	L-Cu	93.2
6	L-Zn	98.3

Table No.2: Larvicidal activity of ligand and their Coper (II) complex in various concentrations

S.No	Compounds	Concentration(ppm)	Mortality rate at different time intervals (%)				
			12 hr	24 hr	36 hr	48 hr	60 hr
1	L	25	0	10	15	25	35
		50	10	15	35	40	55
		100	15	25	40	45	60
2	L-Cu	25	10	15	25	30	40
		50	20	35	45	65	90
		100	25	45	60	90	100

Table No.3: Cytotoxicity of Schiff base (L) and its Zn(II), Cu(II), Co(II) and Mn(II) metal complexes on MCF-7 and K-562 cancer cell lines

S.No		% Control Growth							
		Drug Concentrations (µg/ml)							
		Human Breast Cancer Cell Line MCF-7				Human Leukemia Cell Line K-562			
1		10	20	40	80	10	20	40	80
2	L	22.6	11.9	27.4	21.1	-8.9	-2.2	20.6	29.3
3	L-Zn	22.5	16.6	19.0	36.2	4.8	10.2	33.8	45.1
4	L-Cu	53.3	53.6	44.7	52.9	11.6	34.8	58.7	84.8
5	L-Co	17.6	15.7	17.0	21.9	18.8	56.1	48.9	77.7
6	L-Mn	38.8	32.1	20.4	40.7	2.3	3.4	18.8	19.9
7	ADR	20.3	5.9	3.5	2.8	-22.3	-16.0	-7.4	15.0

Table No.4: Cytotoxicity of Schiff base ligand, L and its Zn(II), Cu(II), Co(II) and Mn(II) metal complexes on MCF-7 and K-562 cancer cell lines

S.No		Human Breast Cancer Cell Line MCF-7			Human Leukemia Cell Line K-562		
		LC_{50}	TGI	GI_{50}*	LC_{50}	TGI	GI_{50}*
1	L	NE	NE	<10	NE	NE	<10
2	L-Zn	NE	NE	<10	NE	NE	<10
3	L-Cu	NE	NE	NE	NE	NE	NE
4	L-Co	NE	NE	<10	NE	NE	33.8
5	L-Mn	NE	NE	<10	NE	NE	<10
6	ADR	NE	NE	<10	NE	NE	<10

Value GI50* of <10µg/ml-superactive, 10-15 µg/ml- moderately active, 15-30 µg/ml- Weakly active, 30-80µg/ml-Resistant, >80µg/ml- inactive

GI50= Concentration of drug causing 50% inhibition of cell growth, TGI= Concentration of drug causing total inhibition of cell growth, LC 50=Concentration of drug that 50% of the cells, NE-Non evaluable data, ADR= Adriamycin (Doxorubicin, Positive control drug).

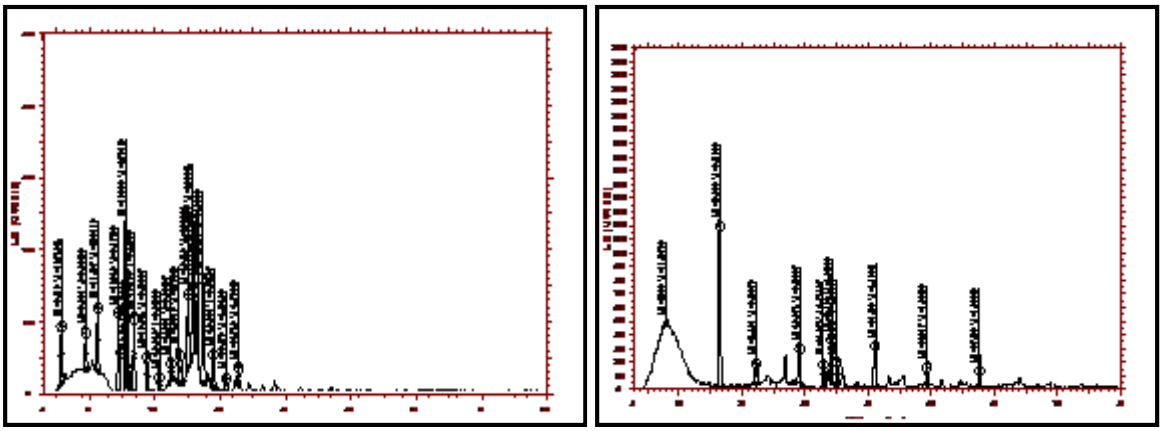


Figure No.1: Powder XRD pattern of ligand L and its Cu (II) complex

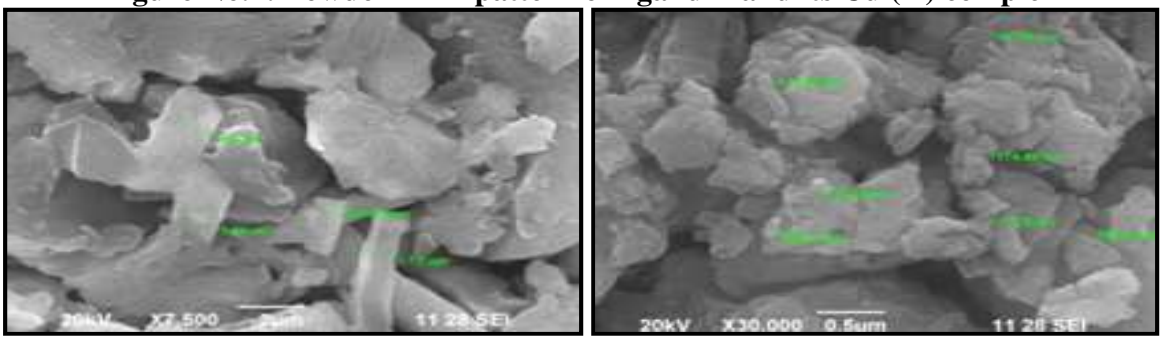


Figure No.2: SEM images of Ligand and Cu (II) complex

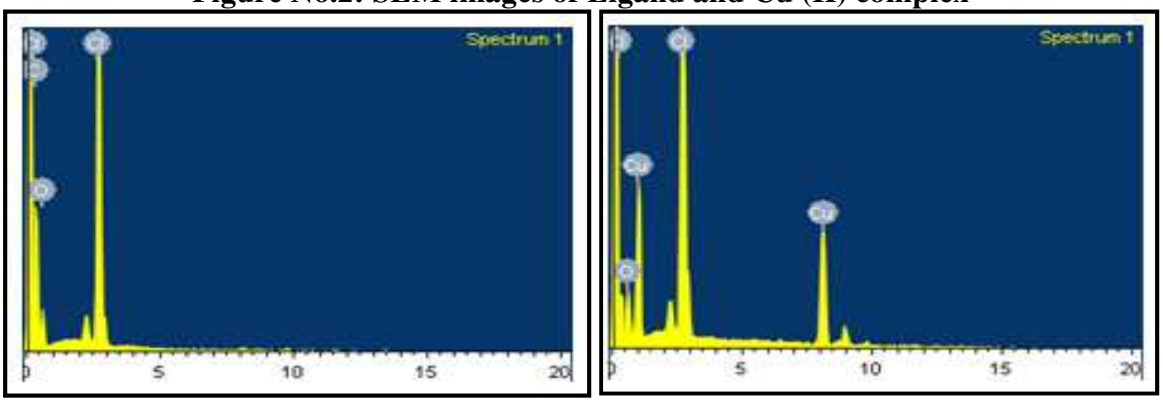


Figure No.3: EDAX images of Ligand and Cu (II) complex

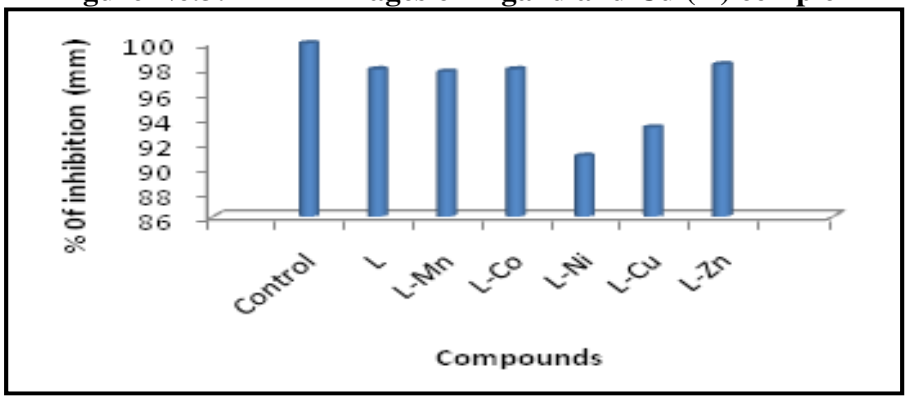


Figure No.4: Bar diagram representation of antioxidant activity

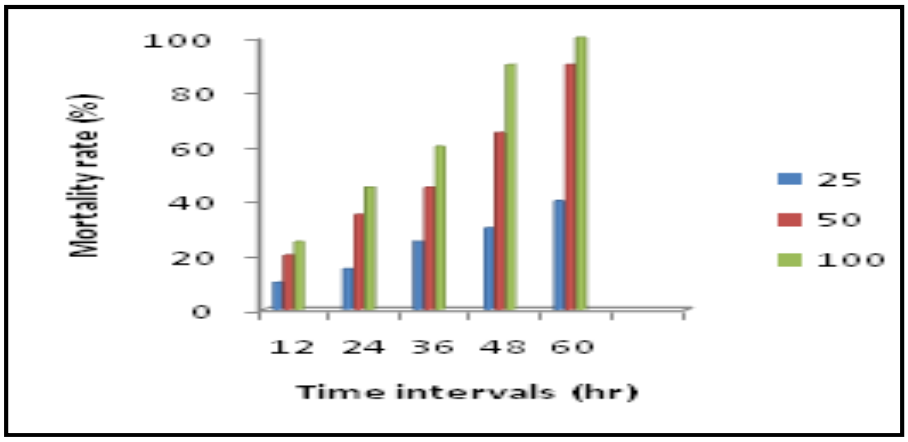


Figure No.4: Larvicidal activity of ligand and their Coper (II) complex in various concentrations

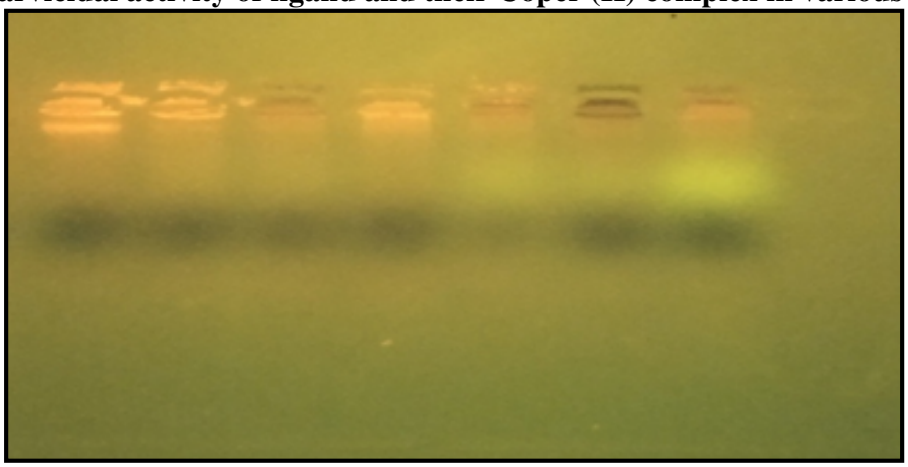
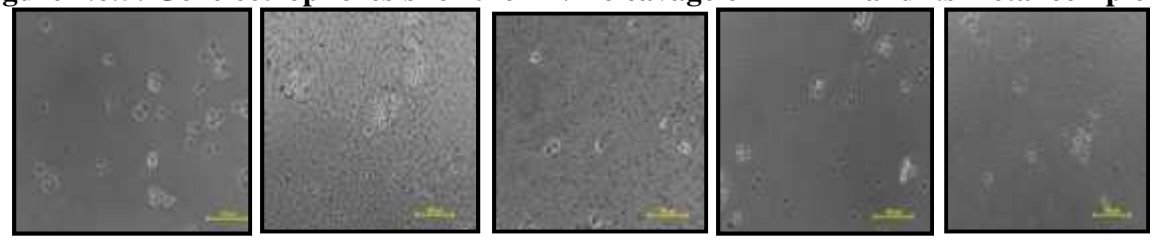
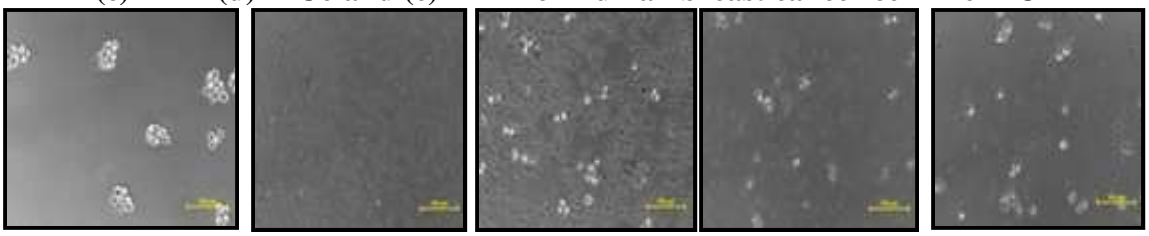


Figure No.5: Gel electrophoresis for the DNA cleavage of HYMP and its metal complexes



(a) (b) (c) (d) **(e)**

Figure No.6: Anticancer activity; Images of Ligand and metal complexes (a) Reference (b) L (c) L-Zn (d) L-Co and (e) L-Mn on human breast cancer cell line MCF-7



(a) (b) (c) **(d)** **(e)**

Figure No.7: Anticancer activity; Images of Ligand & metal complexes (a) Reference (b) L (c) L-Zn (d) L-Co and (e) L-Mn on human Leukemia cancer cell line K-562

CONCLUSION

In this study, a Schiff base ligand (Curcumin and semicarbazide) was synthesized. They formed stable complexes, 2:1(L:M ratio) with transition metal ions such as Zn(II), Cu(II), Ni(II), Co(II) and Mn(II). The synthesized compounds were characterized by XRD and SEM-EDAX analysis. They are also tested for antioxidant and larvcidal activity. The XRD and SEM analysis explains the nanocrystalline structure of the compounds. EDAX studies gives information about metal purity and elemental composition. Antioxidant studies reveal that most of the synthesized compounds have potential antioxidant activity. The larvicidal activity of copper complex showed increased mortality rate than the ligand. The DNA cleavage studies revealed that the Co(II) complex has shown complete cleavage of genomic DNA of Basillus. Finally the anticancer activity of the ligand (L) and its Mn(II), Co(II), Cu(II) and Zn(II) Complexes was determined by sulforhodamine -B assay on human breast cancer cell line MCF-7 and human Leukemia cell line K-562. Results revealed that the ligand (L) and its complexes are super active on human cancer cell lines MCF-7 and K562 when compared with reference ADR.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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