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Advancing Metallo pharmaceuticals Structural, Spectroscopic, and Bio-functional Studies of a Copper (II)–Curcumin Hybrid

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ABSTRACT

By condensing 1,7-bis (4-hydroxyl-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (Curcumin) with thiosemicarbazide hydrochloride, a schiff base ligand (L) generated from curcumin was produced. Multiple spectroscopic methods, including UV-Vis, FT-IR, XRD, and TGA, were used to analyze the synthesized copper complex of ligand [L]. We know that the copper complex is not an electrolyte because of its molar conductance value. Up to 600°C, the copper complex remained stable, according to thermogravimetric research. Microanalytical measurements corroborated the (1:1) copper:ligand stoichiometry of the produced Cu complex, and UV-Vis spectral studies assigned the square planar shape to the Cu (II) ions. The antibacterial and antioxidant activities of the ligand and its copper complex were studied, and the findings revealed that the Cu (II) complex exhibited significantly stronger actions than the ligand alone. Results from in vitro cytotoxicity tests on human breast cancer cell lines (MCF-7) indicate that the synthesized compounds have moderate to good cytotoxic capability.

KEYWORDS: *Schiff base, Curcumin, Copper (II) complex, antibacterial, antioxidant, cytotoxic activity*

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1. INTRODUCTION

Traditional medicine has long relied on plant and extract-based remedies for a wide range of illnesses [1,2]. Transition metal complexes are vital in both the medical and agricultural fields [3]. Analgesic, anti-inflammatory, anti-allergic, antioxidant, antifertility, anti-proliferative, antiviral, and antibacterial metal complexes based on Schiff bases. [4-6]

Curcumin, a yellow pigment, is the active ingredient of turmeric, an Indian spice also known as curcuma longa, that is used in daily cooking. The primary ingredient of naturally occurring curcumin is a typical substituted [illegible]-di-ketone that primarily resembles acetyl acetone [7]. The compounds that have drawn and continue to draw the greatest interest from scientists at the present time are curcumin and its derivatives, as well as its synthetic analogues and the many types of in-house manufactured metal complexes [8,9]. Up to a daily dosage of 12–14 g for an adult, curcumin has been determined to be harmless to humans [10]. Traditional Chinese and Ayurvedic medicine have made extensive use of it for over four thousand years due to its long-standing reputation for medical efficacy. Curcumin has a reputation as a blood purifier in Ayurveda, and it has only lately been discovered that it may chelate with various metal ions, reducing their buildup in the human body.

Depending on the solvent, curcumin may exist in a variety of conformations and display its keto-enol tautomerism. Because of the strong intramolecular hydrogen bonding, the enolic isomer form is much more stable than the keto form [11]. Naturally occurring curcumin molecules are hydrophobic because they are extremely poorly soluble in water at physiological pH [12]. In order to enhance its biological activity and medicinal benefits, it is necessary to increase its bioavailability and make it more soluble in water and other nontoxic solvents. This is because its metabolism is rapid, absorption is limited, excretion is also limited, serum levels are low, and tissue distribution is also limited [13,14]. In order to increase the drug's bioavailability and solubility, several synthetic routes of curcumin have been suggested. These include conjugating curcumin to a water-soluble polymer [15] or encapsulating it in a colloidal carrier that contains silver nanoparticles [16], gold nanoparticles [17], and polymeric nanomaterials [18]. This process involves turning the target compounds into salt forms by inserting or attaching a thiosemicarbazide group as a substituent on the aromatic ring in curcumin. This boosts its water solubility [19]. An appealing area of study for inorganic researchers is the production of curcumin coordinated copper complexes, which is a very successful method for increasing the bioavailability of the curcumin moiety [20]. Numerous curcumin complexes have been discovered in the literature, indicating much greater stability than the free curcumin molecule [21,22]. The stability of the curcumin molecule is much enhanced when the Zn (II) ion complexes with the curcumin moiety at a pH 7 buffer [23]. There are two main benefits to using stable curcumin coordinated metal complexes: first, the compounds become more soluble after successfully complexing with the metal ions, and second, the complexes act as antioxidants, reducing the toxic power of the metal ions in question [24]. The apoptosis signal transduction pathway is overcome by the compounds' increased aqueous solubility, which draws our attention towards the future possibility of potent anticancer agents based on curcumin. This is demonstrated by the enhanced cytotoxicity on prostate cancer cell lines observed when curcumin complexes with Palladium (II) ions, including their conjugation to additional functionalized biologically active ligating moiety [25]. The metal complexes of Cu(II) and Zn(II) ions garnered greater attention because to their extensive and varied biological or biomedical uses, however there are many documented transition metal complexes of curcumin [26]. According to previous investigations, a Cu-curcumin complex is formed when Cu (II) interacts with curcumin. This combination has anti-amyloid [27] and anti-cancer [28] characteristics. Results show that Cu-curcumin complexes are more powerful with recyclable activity than Zn-curcumin complexes [29], after their successful synthesis and testing for antioxidant activities in 2015. Biological imaging/radio-imaging, DNA intercalating, antiviral, anti-HIV, anti-arthritic, and antimicrobial/antifungal activities were observed in the metal complexes coordinated by curcumin [30]. In light of the above, we provide here the details of a novel Schiff base ligand that incorporates a thiosemicarbazide moiety and its copper (II) complex, produced from curcumin. Additionally, the antibacterial, antioxidant, and anti-inflammatory characteristics of the produced compounds were assessed.

2. EXPERIMENTAL:

2.1 Material & methods:

All of the solvents and Curcumin required to make the ligand and copper complex came from Merck; everything else, with the exception of Curcumin, came from Hi-media and did not undergo any further purification before usage.

The newly synthesized compound's elemental analyses were acquired using a Perkin Elmer CHN 2400 analyzer from CIF, CDRI, Lucknow (U.P.). The chemical potential of the copper complex was assessed using a Systronics type 302 conductivity bridge, which was calibrated at 25±0.01°C using a millimole solution in DMSO. We used a 1 cm quartz cuvette and a DMSO Perkin Elmer UV-Vis spectrophotometer at the PC ray research center at ITM University in Gwalior to capture electronic absorption spectra at ambient temperature. With the use of KBr pellets, the compound's infra-red spectra were recorded using a Perkin Elmer-2400 FTIR spectrophotometer at the PC ray research facility at ITM University, Gwalior, within the 4000-400 cm-1 range. A JEOL GSX-300 MH2 FX-1000 spectrometer was used to conduct H1 NMR experiments on the ligand and its Cu(II) complex in DMSO -D6, with TMS (Tetra methyl silane) serving as an internal standard. An examination was performed to estimate the contents of chloride ions [32] and copper ions [31] using gravimetric and volumetric methods, respectively. The thermal analyzer (TGA/DSC) at Jiwaji University, Gwalior, India, was a Shimadzu model operated in an inert N2 environment with alumina power serving as a reference. Information on copper complex X-ray diffraction patterns (XRDs) and other relevant data has been gathered from the CIF at Jiwaji University Gwalior.

2.2 Chemistry:

2.2.1 Synthesis of Schiff Base ligand

Stirred in a heated environment for one hour was a solution of curcumin (1g, 3.0 mmol) in 50 ml of methanol. After stirring the curcumin solution thoroughly, thiosemicarbazide hydrochloride (0.93g, 1mmol) was added drop by drop, and the mixture was refluxed for 6 hours. Thirty minutes after adding TSC, the reaction mixture's color changes from light yellow to a thick brownish precipitate. At last, a thick precipitate forms as the reaction mixture undergoes a transformation from a light yellow to a dark brownish color. The next step was to boil out half of the reaction mixture using a hot plate, let it sit overnight, filter it with whatman filter paper, wash it many times with ether and methanol, and then put it in a desiccator for the night.

2.2.2 Synthesis of Copper (II) Complex from Schiff base ligand

Appropriate methods have been developed to produce a significant yield employing copper salt in order to create the Copper(II) complex of Schiff base ligand. Drop by drop, the copper salt was added to the hot stirred methyl ester solution of the ligand in a 1:1 molar ratio after dissolving in a small quantity of methanol. Once the addition was effective, the reaction mixture was allowed to stir continuously with reflux for four to five hours. After the solid precipitate underwent a color shift, it was filtered out and washed many times with ether and methanol. In Fig1-, we can see the structural representation of the proposed complex after letting the colored precipitate dry at room temperature. Scheme 2 shows the experimental setup that was employed to manufacture the copper(II) complex. Tabulated in Table 1 are the obtained yield, composition, color molar conductance values, and empirical formula.

Table 1: Physicochemical Properties of ligand and its Cu(II) Complex:

S. N.	Compound	Colour	Melting point	Molecular weight	Molar Conductance	Analysis(%) Found				ʎ Max
						C%	H%	N%	Cal. Cu%	
1.	$[C_{24}H_{31}O_5N_3S]$ Schiff base ligand	Yellow	149±2° c	863.96	18.5	62.10 (62.20)	5.29 (4.40)	9.78 (9.80)	-	320nm
2	$Cu[C_{45}H_{22}O_{10}N_6S_2]$ Cu(II) Complex	Dark Green	181±2° c	921.5	1.9	56.78 (56.81)	5.0 (4.84)	9.12 (9.05)	7.46 %	215nm

2.2.3. Synthesis of Copper NPs from Copper (II) Complex:

Appropriate methods have been developed to produce a significant yield employing copper salt in order to create the Copper(II) complex of Schiff base ligand. Drop by drop, the copper salt was added to the hot stirred methyl ester solution of the ligand in a 1:1 molar ratio after dissolving in a small quantity of methanol. Once the addition was effective, the reaction mixture was allowed to stir continuously with reflux for four to five hours. After the solid precipitate underwent a color shift, it was filtered out and washed many times with ether and methanol. In Fig1-, we can see the structural representation of the proposed complex after letting the colored precipitate dry at room temperature. Scheme 2 shows the experimental setup that was employed to manufacture the copper(II) complex. Tabulated in Table 1 are the obtained yield, composition, color molar conductance values, and empirical formula.

2.2.4. Antioxidant activity of Schiff base ligand and its Cu (II) Complex:

Methods for testing free radical scavenging capacity were carried out in accordance with the previously detailed procedures developed by Brand-(38) William. The concentration of 5, 10, 15, and 20 µm in DMSO was achieved by diluting a freshly made stock solution (1mg/ml) of the ligand and its copper complex. A beaker was used to combine 3.0 ml of the ligand and copper complex with 1 ml of the methenolic solution of DPPH (2,2- diphenyl-1-picrylhydrazyl) at a concentration of 0.3 mmol. The blank solution was prepared by adding 1 milliliter of methanol to 3.0 milliliters of test samples. The 1 ml DPPH solution and 3 ml DMSO that made up the negative control. After allowing the solution to sit at room temperature for 30 minutes, we measured its absorbance at 517 nm. The test compounds' percentage scavenging capacity was determined using the following equation.

Percentage scavenging ability = $[Ac - \frac{As}{Ac}] \times 100$

“where,

Ac = Absorbance of blank Sample

As =Absorbance of test Sample

The DPPH solution in methanol (1ml, 0.3 mmol) was used as control. In this study, ascorbic acid used as positive control”.

2.3 Biological/ Pharmacology:

2.3.1 Antibacterial activity of Cu (II) Complex and its CuS NPs:

All experiments evaluating free radical scavenging ability followed the protocols laid forth by Brand-(38) William. A newly prepared stock solution (1mg/ml) of the ligand and its copper complex was diluted to obtain concentrations of 5, 10, 15, and 20 µm in DMSO. The ligand and copper complex, 3.0 ml, and the methenolic solution of DPPH (2,2- diphenyl-1-picrylhydrazyl), 1 ml, all in a beaker, were mixed to a concentration of 0.3 mmol. A blank solution was made by mixing 3.0 mL of test samples with 1 mL of methanol. The 1 ml DPPH solution and 3 ml DMSO that were used for the negative control calculations. We took the absorbance reading at 517 nm after the solution had been sitting at room temperature for half an hour. The following equation was used to obtain the % scavenging capability of the test substances.

2.3.2: Anti Inflammatory activity of Schiff base ligand and its Cu (II) Complex:

The reaction mixture was composed of 0.5 mL of bovine serum albumin (3% aqueous solution) and 0.45 mL of compounds with different concentrations (25, 50, 75, 100 µg/mL of final volume). A little quantity of 1 N hydrochloric acid was used to adjust the pH to 6.3. After 20 minutes of incubation at 37°C, the samples were subjected to 2 minutes of heating at 80°C. Each tube was supplemented with 2.5 mL of phosphate buffer saline (pH6.3) after the samples had cooled. Spectrophotometer readings taken at 416 nm indicate the absorption. As a typical medication, diclofenac sodium is used. The experiment was carried out three times. So, here's how we determined the percentage inhibition of protein denaturation:

“Percentage inhibition % = [(Abs (control) - Abs (sample)/Abs(control)] X100

Where,
Abs control = Absorbance of blank sample
Abs sample =Absorbance of test samples”

3. RESULTS AND DISCUSSION:

In addition to being fully soluble in DMF and DMSO, the synthesised Cu (II) complex and CuS nanoparticles were stable at normal temperature. Despite several efforts, we have not been able to produce even a single crystal of the copper (II) complex. Thermogravimetric and differential scanning chromatography (TGA/DSC) has been used to speculate on the thermal degradation pattern of a freshly produced copper complex. You can validate the synthesis of the copper complex by looking at the NMR spectra, which show the distinctive bands and their positions. The location of electronic absorption bands in UV-Visible spectra and molar conductance values have validated the geometry around Cu (II) ions after complexation with curcumin and thiosemicarbazide hydrochloride. The electronic spectra of the Cu(II) complex provide more evidence of the complex's square planar structure. Use of XRD allowed for the estimation of crystallinity, unit cell parameter, and surface morphology. Use of conventional procedures and methods allowed for the testing of cytotoxic, anti-inflammatory, antioxidant, and antibacterial effects. Table 1 shows the ascribed composition based on elemental analysis of the ligand and Cu(II) complex.

Table 1: Physico-chemical Properties of ligand and its Cu(II) Complex:

S. N.	“Compound	Colour	Melting point	Molecular weight	Molar Conductance	Analysis(%) Found				ʎ Max
						C%	H%	N%	Cal. Cu%	
1.	$Cu[C_{45}H_{22}O_{10}N_6S_2]$ Cu(II) Complex	Dark Green	181±2º c	921.5	1.9	56.78 (56.81)	5.0 (4.84)	9.12 (9.05)	7.46 %	215nm ”

The fact that the synthesized copper complex had a low molar conductance value at ambient temperature in DMSO solvent at a concentration of 1×10^2 mol/L suggested that it was not electrolytic in nature. We used kjeldhal's technique to find the nitrogen content of the complex, and we used iodometric volumetric measurement using potassium iodide and standard sodium thiosulate solutions to find the proportion of copper metal in the copper (II) complex.

The synthesised Cu(II) complex dissolved entirely in ethanol, dimethyl sulfoxide (DMSO), and DMF, but it did not dissolve in water. Within ±0.5% of C, H, N, O, and S, there were elements of the synthesized Cu(II) complex. Nanoparticles of copper and copper complex were stable in air and melted at high temperatures.

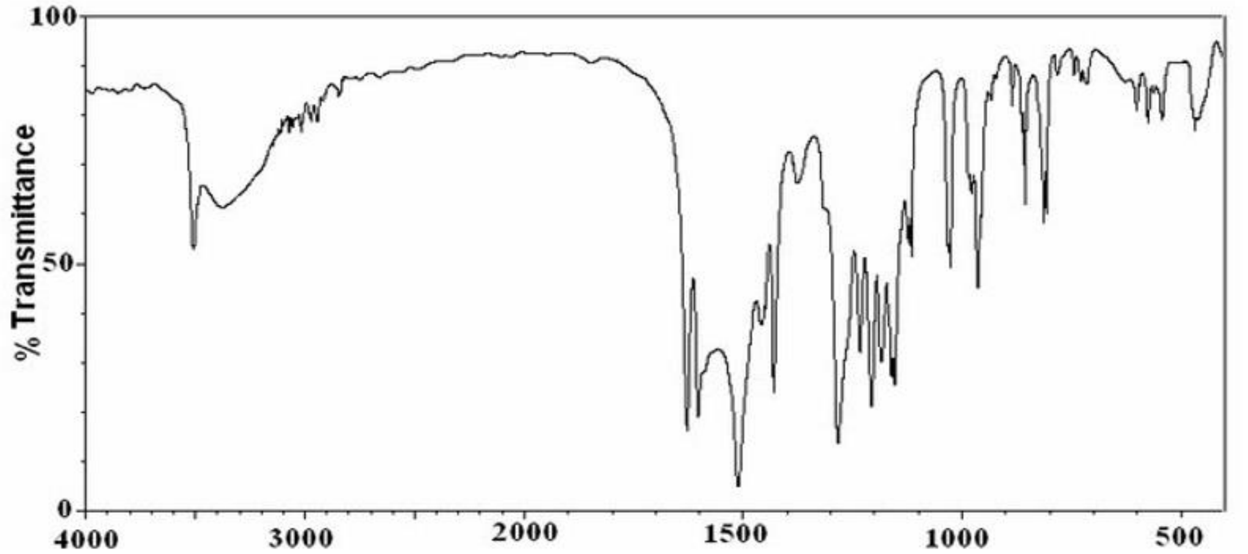

Fig-1: Structure of Schiff base ligand and its Copper (II) complex with curcumin moiety

3.1: Stability of Curcumin coordinated Cu (II) Complex:

The cytotoxic efficacy against tumors is affected by the stability of metal complexes; hence, the hydrolyte stabilities of Cu(II) complex were studied using a UV-visible spectrophotometer. Spectra show the ultraviolet-visible absorption of Cu (II) complex in DMSO solvent (TBS, PH-7.4, 1%DMSO) at 0, 24, and 48 hour intervals. The synthesised copper complex remained stable up to 48 hours, since the UV-visible spectra of the complex do not appreciably deviate from those reported under laboratory circumstances.

3.2: Molar Conductance:

The molar conductance of the copper complex containing curcumin that was produced was measured at room temperature in DMSO with solutions comprising 10-3 M. Copper (II) complexes are not electrolytes, according to their molar conductance values [34].

3.3 Infrared spectra:

Infrared spectroscopy was used to study the structural characteristic of the Schiff base ligand, Cu (II) complex and its NPs, which are produced from curcumin. Due to (N-H) stretching vibrations, which may overlap with hydrogen-bonded O---H vibrations, the ligand's infrared spectra display a wide band of medium intensity at 3472 cm-1 [35]. A band of medium intensity at 3216 cm-1, which is thought to represent the benzene ring system's N-H stretching vibrations. The distinctive medium intensity band at 1606 cm-1 is a result of the azomethine group's v (C=N) vibration. For example, an aromatic ring may be seen as a band at 1436 cm-1. Its copper complex and the ligand's infrared spectrum data are shown in table 2.

Table 2: IR spectral data of ligand and its copper complex and its NPs (cm-1):

“Compound	ν (O-H)	ν (C=C)	ν (C=S)	ν (OCH3)	ν (C=N)	ν (C-N)
[($C_{24}H_{31}O_5N_3S$)] Schiff base ligand	3472	1513	813	1026	1604	-
[Cu($C_{45}H_{22}O_{10}N_6S_2$)$_2$]	3290	1528	840	1378	1678	440
NPs	3395	1595	940	1401	1595	940”

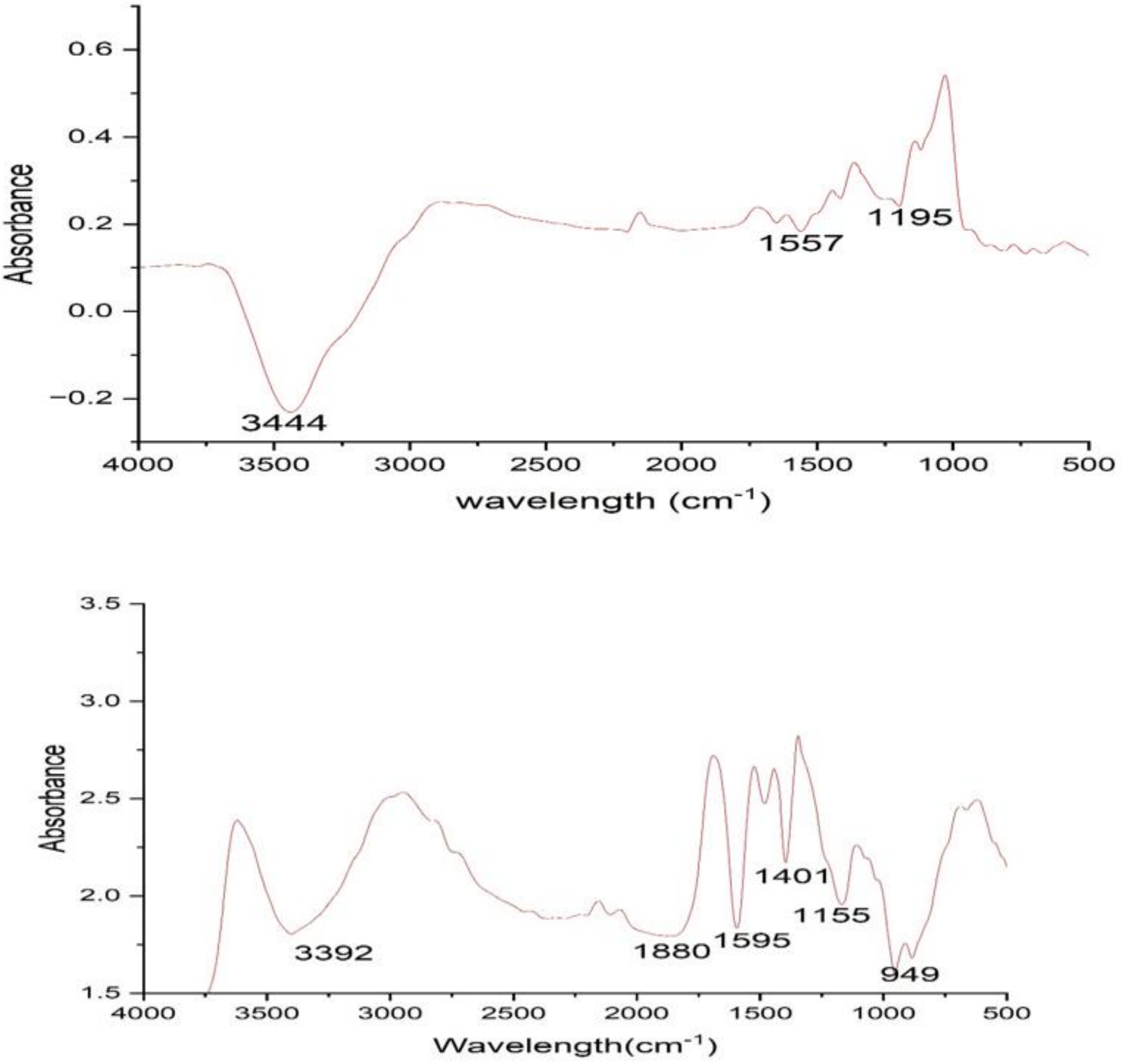

Fig- 2: FT-IR Spectra of Schiff base ligand Cu(II) Complex and its NPs

The presence of a new, sharp band at 1678 cm-1, which is ascribed to the ν (C=N) band, and the elimination of the carbonyl band in the spectra of the Schiff base copper complex (II) support its development. The spectra of copper complexes show that nitrogen and sulfur are closely related to copper metal, as the bands corresponding to -NH and C-S moved to higher frequencies by 12-60 cm-1 [36]. The coordination of the C=S group of thiosemicarbazide is shown by the band at 813 cm-1 being displaced to a lower frequency in the spectra of the copper complex, around 10-40 cm-1. According to reference [37], the copper complex has low-intensity non-ligand bands at 616 cm-1 and 440 cm-1, which are attributed to the stretching frequencies of the ν (Cu-S) and ν (Cu-N) bands, respectively. The spectra of the unbound ligand did not show these bands, which proved that the S and N atoms were involved in the coordination. The ligand and its Cu(II) complex were shown in the IR spectra in figure 2. Furthermore, as can be seen in figure 2 of the Cu nanoparticles' spectra, there is a small absorption band at 3392 cm -1 that represents the stretching vibrations of the O-H bonds in the H 2 O molecules adsorbed onto the surface of the nanoparticles. The stretching vibration of the C=O group is responsible for the bands seen at around 1880 cm-1 [17, 18, 26]. The nitro group's stretching vibration is seen at modest absorption peaks at 1591 cm-1 and 1401 cm-1. The stretching vibrations of C-F were shown by the band at 1155 cm-1, whereas the stretching vibrations of C-Cl were shown by the band at 949 cm-1. [17]

3.4: Electronic Spectra:

The presence of a “new, sharp band at 1678 cm-1, which is ascribed to the ν (C=N) band, and the elimination of the carbonyl band in the spectra of the Schiff base copper complex (II) support its development. The spectra of copper complexes show that nitrogen and sulfur are closely related to copper metal, as the bands corresponding to -NH and C-S moved to higher frequencies by 12-60 cm-1 [36]. The coordination of the C=S group of thiosemicarbazide is shown by the band at 813 cm-1 being displaced to a lower frequency in the spectra of the copper complex, around 10-40 cm-1. According to reference [37], the copper complex has low-intensity non-ligand bands at 616 cm-1 and 440 cm-1, which are attributed to the stretching frequencies of the ν (Cu-S) and ν (Cu-N) bands, respectively. The spectra of the unbound ligand did not show these bands, which proved that the S and N atoms were involved in the coordination. The ligand and its Cu(II) complex were shown in the IR spectra in figure 2. Furthermore, as can be seen in figure 2 of the Cu nanoparticles' spectra, there is a small absorption band at 3392 cm -1 that represents the stretching vibrations of the O-H bonds in the H 2 O molecules adsorbed onto the surface of the nanoparticles. The stretching vibration of the C=O group is responsible for the bands seen at around 1880 cm-1 [17, 18, 26]. The nitro group's stretching vibration is seen at modest absorption peaks at 1591 cm-1 and 1401 cm-1. The stretching vibrations of C-F were shown" by the band at 1155 cm-1, whereas the stretching vibrations of C-Cl were shown by the band at 949 cm-1. [17]

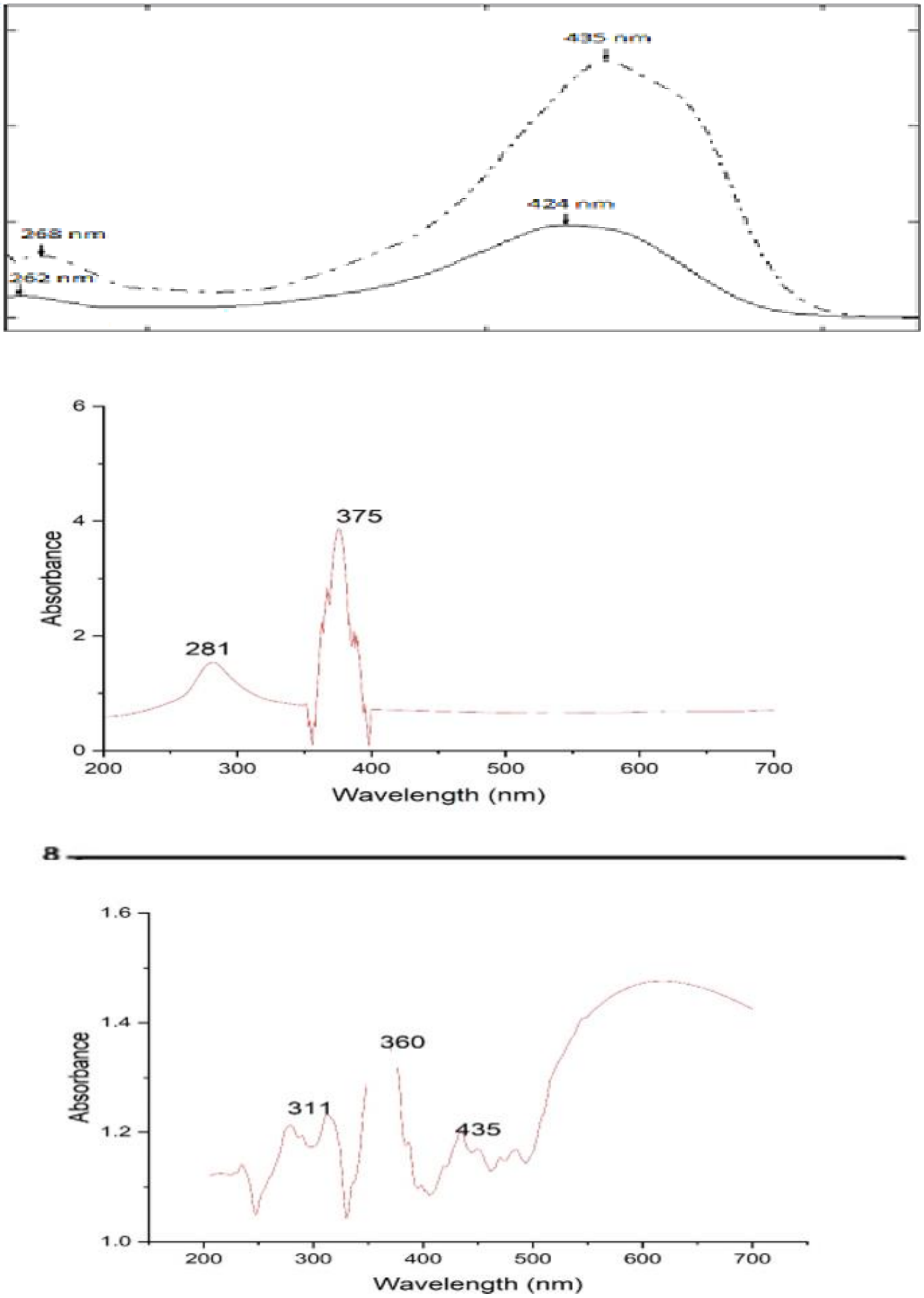

Fig:3: Electronic Spectra of Schiff base ligand, Cu(II) complex and its NPs

3.5: Thermal Studies (TGA/DTA):

Research into the structural and kinetic properties of coordination molecules by thermal breakdown of inorganic metal complexes has recently attracted a lot of interest. Figure 4 shows the three major steps of the breakdown process as shown by the TG-DTA curves of Cu(II) complexes. The existence of lattice water molecules was shown by the DTA curves showing a weight loss of 5.91% at an initial temperature range of 61.58°c [39]. The lack of mass loss in the Cu(II) complex TG curve between 70 and 150 degrees Celsius verifies the fact that no coordinated water molecules are present [40]. As amide and chloride ions are lost, the weight decreases between 160.65°C (27.24%) and 233.43°C (15.22%) as the breakdown temperature approaches. Following a mass loss of 49.69% at a breakdown temperature in the range of 445.46°C (corresponding to the loss of the remaining organic moiety of the ligand), the copper complex is eventually transformed into its oxide [41] fig.4..

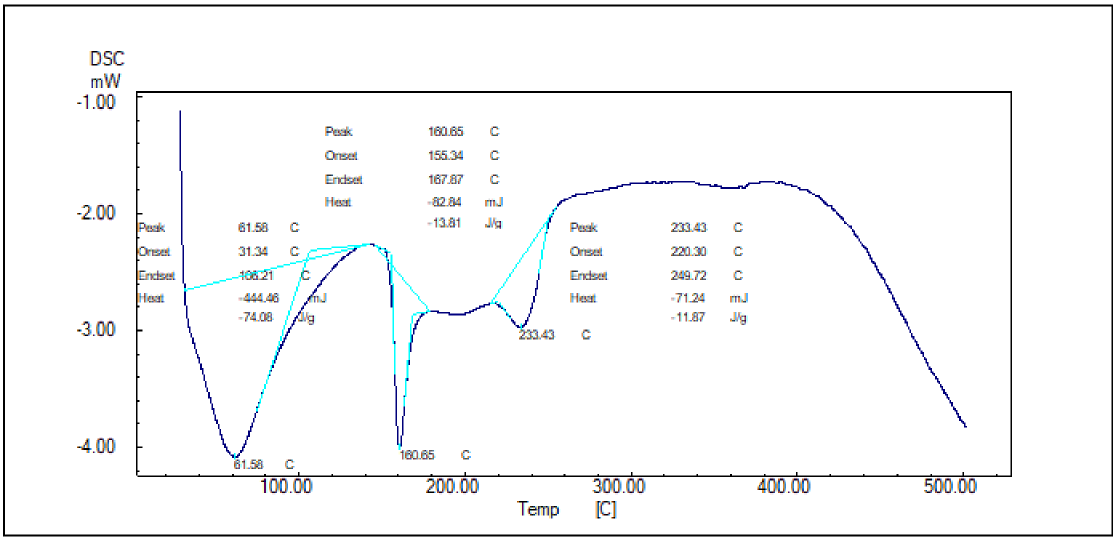

Fig-4: Thermal Studies of Schiff base ligand and Cu(II) Complex.

3.6: X- ray Diffraction analysis:

X-ray diffraction analyses of the produced chemical were carried out at angles ranging from 10° to 80°. Figure 5 displayed the powder XRD patterns of the ligand and its Cu(II) complex throughout the 2θ= 0 - 80°A range. The complex's average crystalline size, d, was determined by XRD with the use of Scherrer's formula [42,43].

“ $d= (0.89\lambda/\beta \cos\theta)$

Where, d= average crystalline size of the phase under investigation
λ= wavelength of X-ray beam used.
β= Full width at half maximum of diffraction
θ= Bragg’s angle”

Since we were unable to produce a single crystal of the Cu(II) complex with the ligand despite our best efforts, we decided to characterize the complex using powder x-ray diffraction (PXRD). Following the failure of the synthesized compound to develop as a single crystal, x-ray diffraction was used to gather more information on the structure of the Cu(II) complex. Copper complexes with ligands exhibit both crystalline and amorphous structures in their x-ray diffraction patterns [44,45]. Ten reflection peaks were detected in the diffraction pattern of the Cu(II) complex within the (2θ) 0° to 60° range, with the highest at 16.343 and a corresponding d spacing value of 5.412 A°. The existence of amorphous components in the complex might explain the PXRD pattern seen in figure 5, which has externally broad low-angle peaks [46,47]. Using the imine N, thiosemicarbazide - S, and enolic - O atoms of the curcumin moiety as a tridentate binding mode, the ligand coordinates the core Cu(II)ion with the deformed octahedral geometry of the copper complex [Cu (C45 H22 010 N6 S2)2]. We find that the average crystalline size of the ligand is 85.77 nm and that of its Cu(II) complex is 78.49 nm based on the XRD patterns that were observed. The size of the particles is reduced after complexation. When looking at the XRD patterns of the ligand and Cu(II) complex, it is evident that copper ions are coordinated to the ligand during complexation since the Cu(II) complex displays additional peaks at 56.80, 62.60, and 66.20 [48]. In Figure 5, we can see the XRD pattern of the Cu NPs. At positions 2θ = (43.67, 50.79 and 74.43), three diffraction peaks were seen.

The synthesized copper nanoparticles ‘were found the amorphous nature confirmed by X-ray diffraction analysis

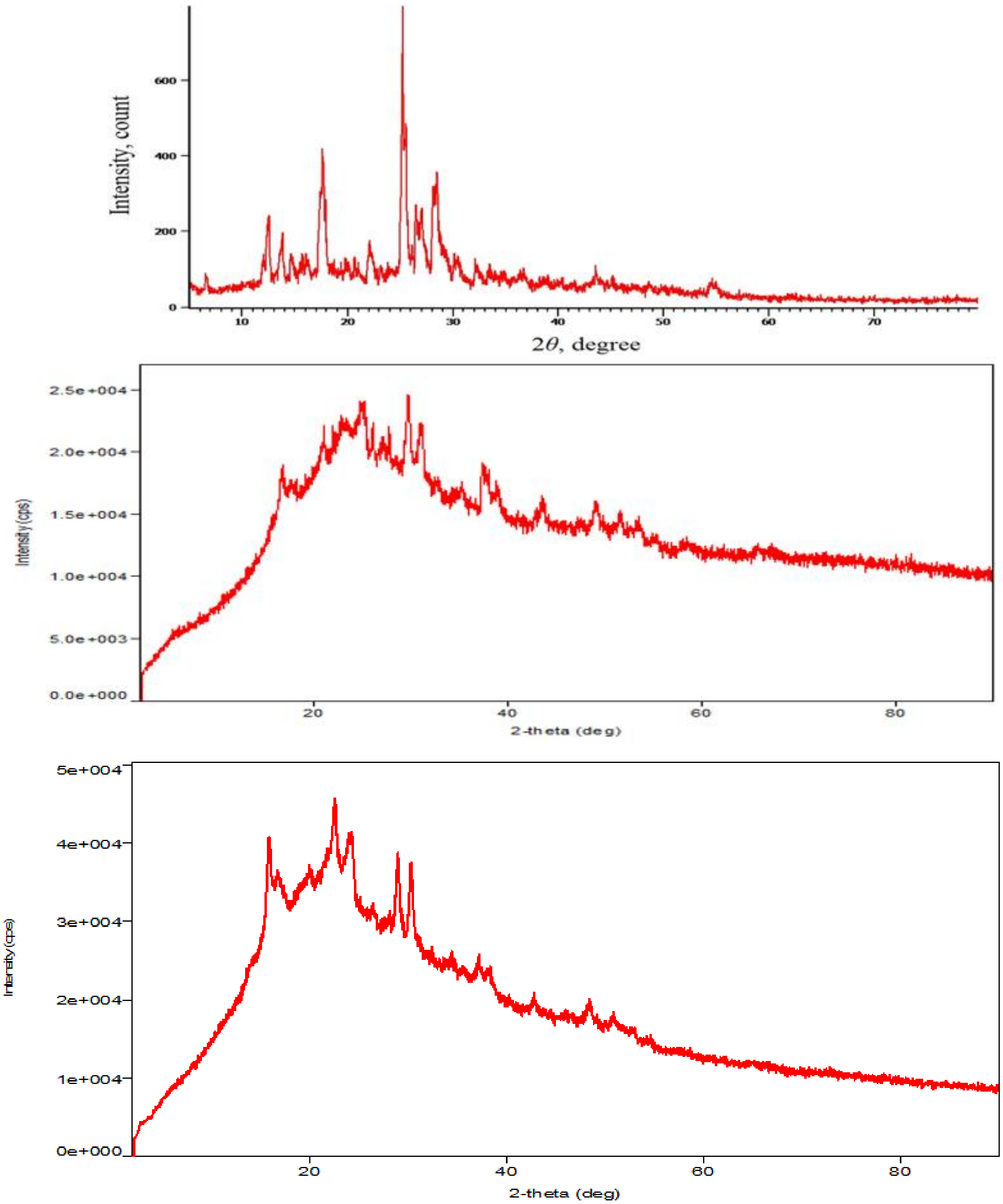

Fig-5: XRD Spectra of Schiff base ligand Cu (II) complex and its NPs

3.7: SEM of Curcumin copper NPs:

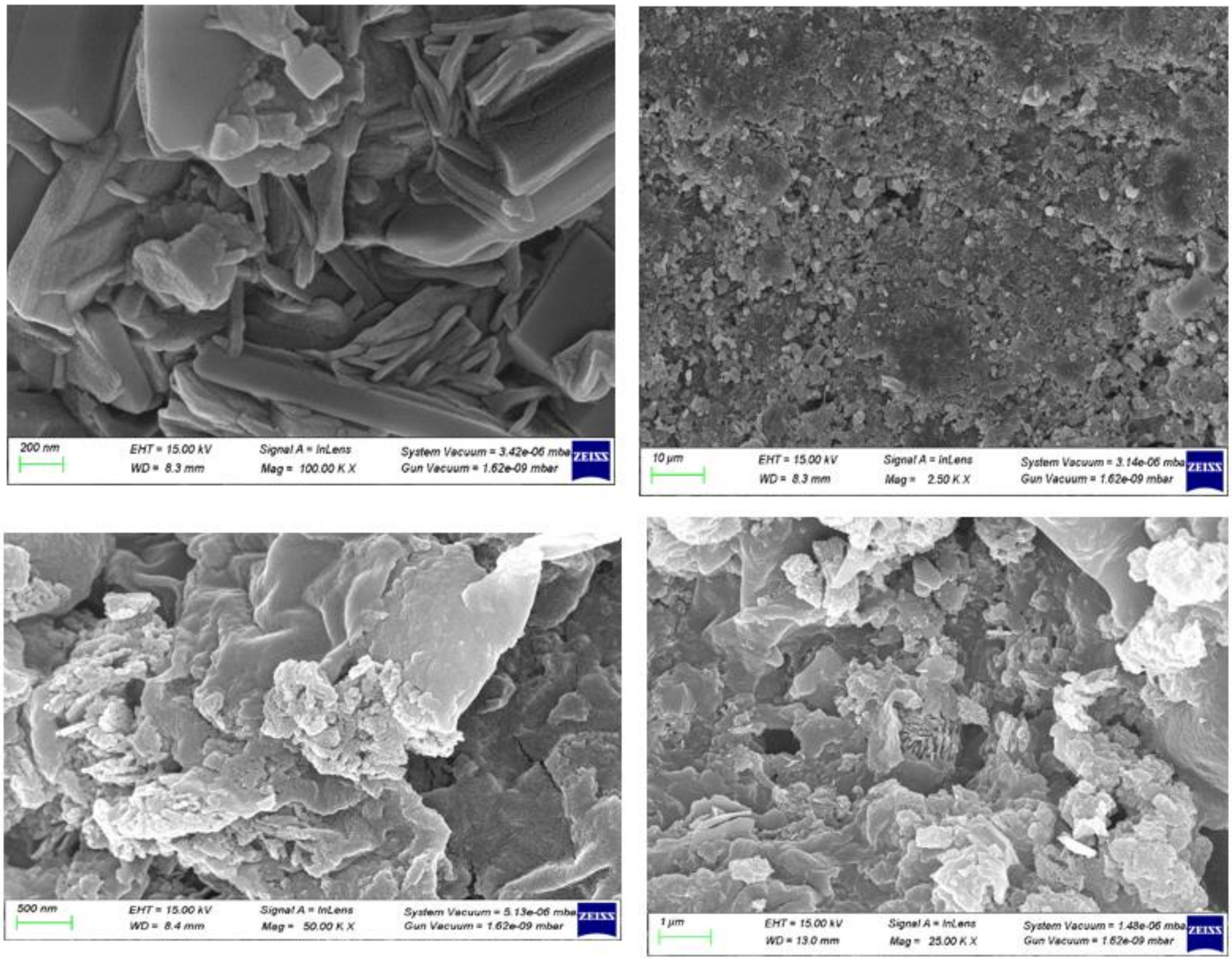

Fig.6: SEM of Curcumin copper NPs

Figure 6 shows a scanning electron micrograph of curvecumin copper nanoparticles made from Cu(II) complex. This environmentally friendly approach revealed a relatively uniform range of particle sizes in terms of surface shape and size for the Cu(II) NPs. Particles of curcumin copper nanoparticles averaged around 20 nm in size. It mostly manifests as round, non-uniform, and widely aggregated particles.

3.8: In-vitro antibacterial activity of compounds

The studied ligand and “its copper (II) complex were examined for their in-vitro antibacterial screening activities against a variety of bacterial species, including E. coli, S. aureus, and K. pneumoniae. In bacteriological investigations, streptomycin serves as a positive control. The compounds were determined to be active when clear zones were seen. Antibacterial activity was shown to be somewhat to somewhat higher in experiments comparing the ligand with its Cu (II) complex. Coordination of nitrogen, oxygen, and sulfur atoms seems to have the most inhibitory effect on microbial development. Both microbial cell impermeability and ribosome variation contribute to the observed heterogeneity in the efficacy of ligand and Cu (II) complexes.

Liposolubility is a key component in controlling antimicrobial action, as per overtone's idea of cell permeability, the lipid membrane encasing the cell preferentially permits the passage of only lipid soluble substances. As a result of orbital overlap between the ligand and copper ions and partial sharing of the positive change between the two, the polarity of the copper ion is lowered when the ligand and copper ions are coordinated. Also, it makes the copper complex more lipophilic and promotes the delocation of л electrons over the whole chelate ring [49]. Because of its enhanced lipophilicity, the complex is better able to penetrate lipid membranes and obstruct the metal binding sites in microbial enzymes. In addition to killing microbes, copper complexes disrupt cellular respiration, which in turn prevents protein synthesis and limits the organism's potential for development. It has been proposed that the antibacterial action of copper (II) complexes with ligands blocks the active sites of microorganisms, hence inhibiting their multiplication process [50,51]. Liposolubility is the primary determinant of antibacterial activity, according to the overtone hypothesis, which explains that the lipid barrier enclosing the cell only allows lipid-soluble substances to get through. The fact that the complex's lipophilicity grows in relation to the bulkiness of the donor groups connected to the copper atom provides an explanation for this trend. The activity level rises in proportion to the bulkiness. The complex's improved biological activity against the studied bacterial strains compared to the free Schiff base ligand is attributed to the influence of sulfur, nitrogen, and oxygen donor atoms in the produced ligand that forms chelates with copper ions [52]. Factors such as the synthesised Cu(II) complex's enhanced antibacterial activity, particle fitness, copper ion size, and the inclusion of bulkier organic moieties may also play a role [53,54]. Solubility, conductivity, dipole moment, cell permeability mechanism (affected by copper ions), and bond length between copper and ligand are additional parameters that enhance activity [55]. In order to interfere with cell wall production, the complex's active sites create hydrogen bonds with the imino group [56]. The antibacterial activity of the copper nanoparticles was tested against both Gram-positive bacteria after curcumin was used to decrease copper to the +2-oxidation state. The results show that reducing the amount of copper nanoparticles in turmeric increases the antibacterial activity of curcumin and that the reverse is also true. Tables 3, 4, and 7 show that, when compared to Schiff base ligand and Cu(II) complex, curcumin NPs exhibit superior antibacterial activity against both Gram-positive and Gram-negative bacteria. Additionally, the inhibition zones of S. aureus, E. coli, and K. pneumonia are larger in Cu(II)" NPs than in either Schiff base ligand or curcumin Cu(II) Complex.

Table-3: Antibacterial activity of Copper (II) complex

S.N	Test Microbes	Diameter of Zone of Inhibition(in mm) at different drug concentrations			
		0.005 µg/ µl	0.010 µg/ µl	0.015 µg/ µl	0.020 µg/ µl
1	E. coli (MTCC-1687)	12	13	14	15
2	K. pneumonia(MTCC-39)	12	13	13	15
3	S. aureus (MTCC-9724)	13	14	15	18
4	Streptomycin (Standard antibiotic)	28	28	27	28

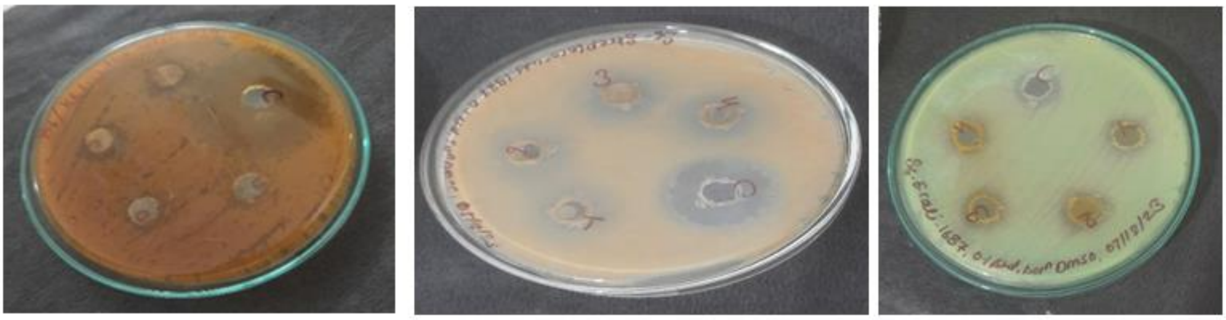

Fig-6: Antibacterial activity of Cu (II) complex

Table-4: Antibacterial activity of Copper (II) NPs:

S.N	"Test Microbes	Diameter of Zone of Inhibition(in mm) at different drug concentrations			
		0.005 µg/ µl	0.010 µg/ µl	0.015 µg/ µl	0.020 µg/ µl
1	E. coli (MTCC-1687)	15	16	17	18
2	K. pneumonia(MTCC-39)	17	18	18	19
3	S. aureus (MTCC-9724)	15	16	18	20
4	Streptomycin (Standard antibiotic)	21	20	21	21"

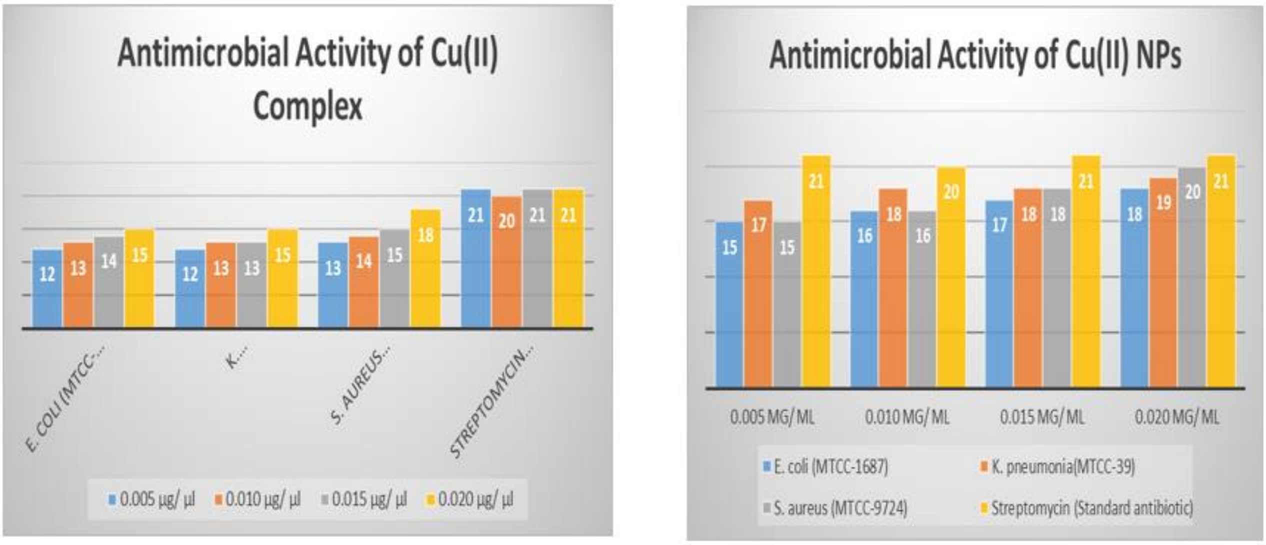

Fig. 7: Graphical representation of Antibacterial activity of Cu(II) Complex and its NPs:

3.9: Anti- inflammatory activity of Schiff base ligand and its copper (II) complex:

It is well-established that "inflammation may be caused by denaturation of proteins. The suppression of albumin denaturation approach, first developed and used by Mizushima et al. [57] with some minor adjustments, was used to study the anti-inflammatory effect of Schiff base copper complex. The chemicals' denaturation-inhibiting capabilities were examined as part of the research into the anti-inflammatory activity's mechanism. This study aimed to explain the findings of an evaluation of the anti-inflammatory activity of a copper complex curcumin that was synthesized from thiosemicarbazide. The inhibitory potential of the copper (II) complex demonstrated that protein denaturation is a concentration dependent process, meaning that the percentage of inhibition increases with increasing concentration, as shown in table.3. It was effective in inhibiting heat induced albumin denaturation at different concentrations. There is a considerable 65.24% inhibition seen in the Cu (II) complex as compared to the Schiff base ligand in this investigation. It is possible that the Cu (II) complex's modest activity is because copper is a metal that readily undergoes oxidation and reduction. Therefore, copper complexes can reduce inflammatory free radicals and hydrogen peroxide [58]. Because of its metabolites, such as imino linkage and phenolic groups, the copper complex" also showed far stronger anti-inflammatory efficacy than the conventional aspirin medicine.

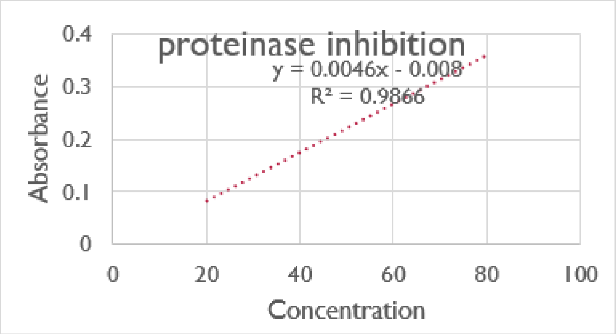

Fig- 8: Percentage inhibition of proteinase activity of Cu (II) complex

Table-4: Anti- inflammatory activity of Schiff base ligand and its copper(II) complex:

S.N	compound	Concentration in µg/ml	Absorption at 210nm	% of inhibition
1.	Aqueous extract of curcumin	100	0.303	64.21%
2.	Schiff base ligand	100	0.314	66.52%
3.	Cu(II) Complex	100	0.321	68.04%

4.	Standard Aspirin drug	100	0.298	63.04%

3.10: Anti-oxidant activity of Schiff base ligand and Cu(II) Complex:

To test if Ligand and its Cu "(II) Complex were antioxidants, the DPPH Assay was used. The radical scavenging action of many chemicals, both natural and artificial, has been extensively studied using DPPH, a stable free radical molecule. The coordinated Cu(II) complex of the curcumin moiety exhibited more antioxidant activity than the Schiff base ligand, according to one study's antioxidant activity data. The study's positive standard for evaluating the antioxidant activity of the chemical was ascorbic acid. The fact that the ligand and its Cu(II) complex have a higher DPPH activity than the curcumin moiety is quite promising. Since the location and number of the hydroxyl group (-OH) and the degree of conjugation of the whole molecule are crucial, the theoretical features are in agreement with the antioxidant activity finding. Antioxidant activity of naturally occurring flavonoids" with comparable conjugation levels is proportional to the total amount of hydroxyl groups present in the benzene ring.

Table- 5: Percentage DPPH free radical inhibition activity by standard ascorbic acid at various concentrations.

"S.No.	Concentration in µg/ ml	Abs.Control in µg/ ml	Absorption of Sample at 517nm	Percentage inhibition	IC50
1	0	0	0	0	50.87%
2	20	0.53	0.459	17.705	
3	40	0.53	0.389	39.027	
4	60	0.53	0.276	59.541	
5	80	0.53	0.147	79.813	
6	100	0.53	0.098	99.909"	

Table-6: Percentage DPPH free radical inhibition activity by Schiff base ligand at various concentrations.

"S.No.	Concentration in µg/ ml	Abs.Control in µg/ ml	Absorption of sample at 517nm	Percentage inhibition	IC_{50}
1	0	0	0	0	59.33%"
2	20	0.53	0.509	75.66	
3	40	0.53	0.451	47.92	
4	60	0.53	0.369	24.90	
5	80	0.53	0.231	13.58	
6	100	0.53	0.142	5.09	

Table-7: Percentage DPPH free radical inhibition activity by Synthesized Cu(II) Complex at various concentrations.

S.No.	"Concentration in µg/ ml	Abs.Control in µg/ ml	Absorption of sample at 517nm	Percentage inhibition	IC_{50}
1	0	0	0	0	61.46%"
2	20	0.53	0.521	1.69	
3	40	0.53	0.438	17.35	
4	60	0.53	0.389	21.60	
5	80	0.53	0.281	46.98	
6	100	0.53	0.233	56.03	

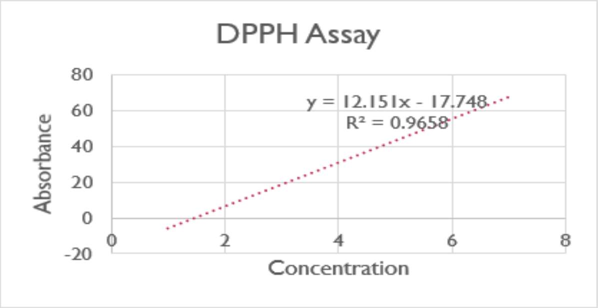

Fig-9: Percentages DPPH free radical inhibition activity of Cu (II) Complex

In order to enhance patients' quality of life, Metallo-drug has recently emerged as a crucial component of therapeutic development. Producing and synthesizing biologically active chemicals with no adverse effects on patients is the primary goal in the fight against pathogenic microbes. In a reasonable application, these complexes might be utilized to cure several common illnesses caused by diverse microorganisms, which is why this notion is important. There are no negative side effects associated with the biological activities of the manufactured curcumin complex, which are comparable to those of several anti-inflammatory, antimicrobial, and antioxidant drugs. The fact that these curcumins coordinated copper complexes are

(1) less hazardous in their natural state
(2) readily curable at low concentrations is the most crucial thing to keep in mind while targeting them.
(3) not causing any bothersome negative effects.
(4) it has to be cheap.

Fifthly, chemically stable and simple to create
Each of these compounds has unique qualities that may be used to great advantage when formulating a new medication. Further in-vivo testing of these manufactured compounds will allow us to determine their precise efficiency. The fact that several of these synthetic curcumin-based Schiff copper complexes display a wide range of prospective health effects comparable to those of current drugs is, without a question, the most intriguing part of them.

4. CONCLUSION:

This research included the synthesis of a new Schiff base ligand combining curcumin and thiosemicarbazide. The resulting Cu (II) combination was stable and had a molar ratio of 2:1. Methods such as electronic spectroscopy, thermal gradient chromatography (TGA/DTA), elemental analysis, molar conductivity, magnetic measurements, and synthetic compound characterization were used. Schiff base ligand coordination to copper atom via azomethine nitrogen, sulfur, and oxygen atoms is shown by infrared spectrum data. Investigating the ligand and its copper complex by electronic spectroscopy revealed that the Cu(II) complex exhibits deformed octahedral geometry. The complex's non-electrolytic nature is supported by its low conductance. A typical empirical formula for the complex is [C_{45} H_{22} $O_{10}N_6$ S_2]. Six coordinated geometries for the copper (II) complex have been identified based on elemental and spectral research. Schiff base ligand and copper complex have been studied for their anti-inflammatory effects. One possible explanation for the higher activity of the Cu(II) complex compared to the free ligand is the high oxidation and reduction potential of copper, as shown by the results. The copper complex exhibited modest antimicrobial activity against the organisms tested, suggesting its potential as a therapeutic candidate after in vivo investigations, thanks to its increased lipid solubility.

5. DECLARATION OF COMPETING INTEREST:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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