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ANTIOXIDANT NOVEL ACTIVITIES OF CURCUMIN COMPLEXES WITH Mg(II), Ca(II), Cu(II), Cr(III) AND Se(IV) METAL IONS: SYNTHESIS AND SPECTRAL STUDIES

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ABSTRACT. Curcumin (Cur) metal complexes of Mg(II), Ca(II), Cu(II), Cr(III), and Se(IV) were prepared and characterized using elemental analysis, molar conductance, IR, UV-spectra, ^{1}H NMR, SEM, TEM, and X-ray diffraction. The very low values of molar conductance confirm that Cl^- ions are absent inside or outside the chelation sphere confirming their non-electrolytic nature, while for Cr(III) Cur is high compared to other curcumin complexes, confirming that Cl^- ions are inside the complexation sphere. Based on IR and electronic spectra, the Cur C=O group in enol form chelated to Mg(II), Ca(II), Cu(II), Cr(III), and tetravalent metal (Se). The surface morphology of the curcumin chelates showed an increase in particle size and irregular grains shaped with an elongated morphology. Transmission electron microscopy revealed that the Cur chelates have spherical black spots like shape with a particle size of 72.21-88.75 nm, 34.89-57.33 nm, and 80.71-100 nm for Cu(II), Zn(II), and Se(IV) Cur respectively. X–ray powder diffraction patterns for Cu(II) Cur complexes showed particle size within 70-90 nm; the antioxidant activities of Cur and its metal complexes were assessed. Results showed that the Cur complexes with Cr, Mg, Ca, Cu, or Se showed potent antioxidant activities. Further studies could evaluate the potency of these complexes to elevate the antioxidant defense system and enhance body functions against degenerative diseases, such as aging, Alzheimer's disease, and viral diseases.

KEY WORDS: Curcumin, Mg/Cur, Cu/Cur, Se/Cur, Electronic spectra, Antioxidant, Oxidative stress

INTRODUCTION

Curcumin (Cur) comes from the *Curcuma longa* rhizomes and has biological and pharmacological characteristics [1]. It has less bioavailability due to its heterogeneity with dist. H_2O [2]. Several methods were used to elevate the bioavailability of curcumin, such as nanoparticles, phospholipids chelate, and inclusion complexes based on cyclodextrin [3].

Nanomaterials have evolved as a promising agent for overcoming the current pandemic infections challenges due to their capacity to decline the formation of biofilms and enhance the antibacterial activity of mixed ligands as more data suggests that transition metals play a vital role in many biological processes, as according to the recorded literature, the interaction between ligands and metal ions may increase the physiological activity of these complexes [4, 5]. Due to the alteration of the nanoparticles' growth, different biomolecules are used to synthesize different nanomaterials. Due to their bioactive surface and conjugation with different nano-formula were more suited for applied biological resources [6].

The biochemical reactions of complexes in the body exposure to many xenobiotics and environmental pollutants result in the excessive generation of reactive oxygen species (ROS) which finally leads to severe oxidative stress under different pathophysiological conditions [7].

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Antioxidants prevent this environmental oxidative stress via free radicals [either singlet oxygen (O·), superoxide radicals (O_2·−), hydroxyl radicals (OH·), or even hydrogen peroxide (H_2O_2)] that adversely change the vital cellular components [7, 8]. Then, the imbalance between free radicals and antioxidants occurs, and thus it is necessary to restore this vital balance for proper physiological functions [8].

Some synthetic antioxidants have been reported to produce toxins or carcinogens [8, 9]. So, the preparation of natural antioxidant alternative sources can be a beneficial natural source to ensure high and sound health [10]. Bioactive compounds of plant origin promote and enhance health by slowing the oxidative stress series and aging procedures, thus preventing many diseases [11].

Curcumin is a polyphenolic compound derived from spice turmeric [12]. The yellow colour of pigments is phenolic and known as curcuminoids, which are present naturally in Cur [13, 14]. Several studies have investigated the diverse immunoprotective effects of curcumin against various immunologically impaired physiological conditions. The therapeutic effect of Cur is anti-oxidative functioning. Cur is a potent antioxidant with phenolic hydroxyl groups as active sites [15-18].

The antioxidant characters of the phenolic (–OH) group where reactive oxygen species (ROS) are present, the activity of electron releasing present on the phenyl ring. The H ion is released due to breaking the O–H bond [19].

Curcumin complexes have many novel and vital characteristics compared to free curcumin: owing to the presence of functional ketone groups bonded with metal ions; thus, the complex curcumin molecules have bioavailability properties. In curcumin metal complexes, the bioactivity of the metal ions has been altered. Cur is a well-mixed ligand, and thus it forms stable complexes with almost all the metal ions [20-21].

The present article aimed to study the chemical structures of Cur complexes with divalent metal ions Mg(II), Ca(II), Cu(II), trivalent metal ion Cr(III) and tetravalent metal ion Se(IV) using elemental analysis CHN, magnetic susceptibility, electronic UV-Vis, molar conductance, IR, ^{1}H NMR, XRD, SEM and TEM analyses, besides testing the antioxidant potency of new synthesized Cur metal complexes to alleviate oxidative injury and reactive oxygen species which is a recent important aim to alleviate the risk of the degenerative diseases.

EXPERIMENTAL

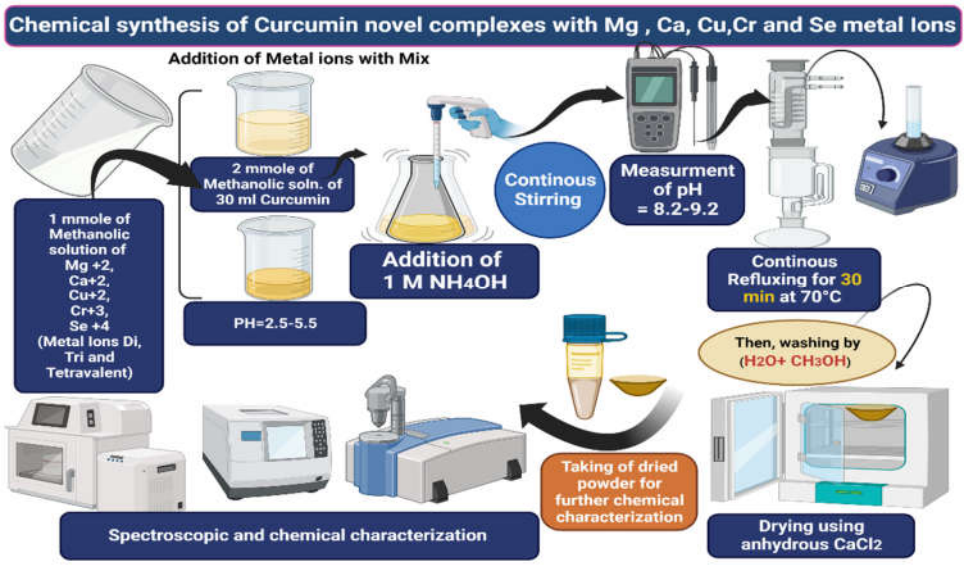
Chemicals

The chemicals used were received from Fluka and Aldrich Companies and were A.R. with a high purity of more than 99.5% for all chemicals used: Curcumin (Cur), magnesium(II) chloride, calcium(II) chloride dihydrate, copper(II) chloride dehydrate, chromium(III) chloride, and selenium(IV) chloride, other chemicals used as it is without purification.

Synthesis of curcumin complexes

Divalent, trivalent, and tetravalent M-curcumin complexes were prepared using H_2O/CH_3OH solution at 70 ºC where the solubility of curcumin is low in the water. The synthesis of curcumin complexes was carried out by adding (1 mmol) $MgCl_2$, $CaCl_2.2H_2O$, $CuCl_2.2H_2O$, $CrCl_3$, and $SeCl_4$ to (2 mmol, 30 mL) methanolic solution of curcumin with molar ratio 1:2 (M(II), M(III) and M(IV):Curcumin). The pH of the resulting solutions ranged from 2.5 to 5.3. By using a solution of 1 M ammonium hydroxide, the pH was adjusted to be within 8.2-9.6 when added to each mixture of curcumin, Mg(II), Ca(II), Cu(II), Cr(III), and Se(IV), to reach to complete chelation. Then make stirring for each mixture, stirring and refluxing at 70 C for 20–30 min. The

product's solid-colored complexes was filtered and washed with a mixture of (water and methanol) several times and finally dried under a vacuum over anhydrous $CaCl_2$, as shown in Scheme 1.



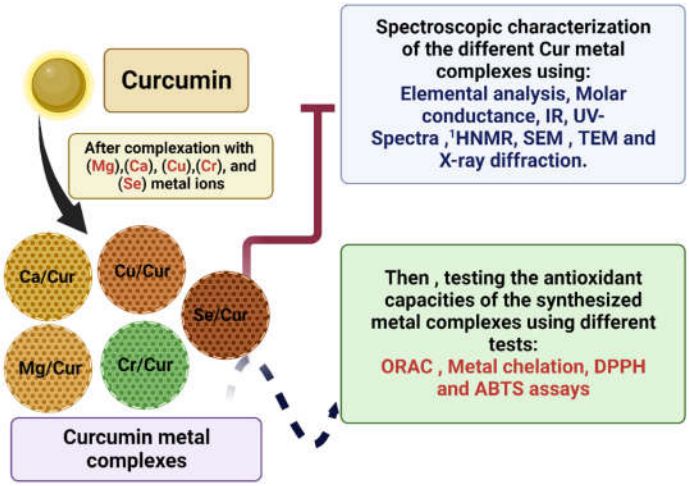
Scheme 1. Chemical synthesis.

Measurements

The elemental analyses C and H were carried out by the microanalysis unit at Cairo University, Egypt, using a Perkin Elmer CHN 2400 (USA). The molar conductivity measurements for curcumin chelates were carried out for a $1x10^{-3}$ mol/cm^3 using dimethylsulfoxide (DMSO) and were measured using the Jenway 4010 conductivity meter. The electronic absorption spectra of Cur complexes were recorded in DMSO solvent within the 800–200 nm range using a UV2 Unicam UV/Vis Spectrophotometer fitted with a quartz cell of 1.0 cm path length. The infrared spectra with KBr discs were recorded on a Bruker FT-IR Spectrophotometer (4000–400 cm^{-1}) at Zagazig University. The ^{1} H-NMR spectra were recorded on a Varian Mercury VX300 NMR spectrometer at Zagazig University. The morphological surface was estimated by a Quanta FEG 250 scanning (SEM) and transmission (TEM) electron microscopes generated at 20 kV accelerating voltage in Mansoura University, where the shapes and sizes of these particles were visualized using a JEOL JEM-1200 EX II and JEOL 100s microscopy, respectively. The X-ray diffraction patterns for Cu(II) curcumin complexes were recorded on X 'Pert PRO PAN analytical X-ray powder diffraction, target copper with secondary monochromatic. After the spectroscopic analysis, the antioxidant capacities will be tested as the graphical experimental design Scheme 2.

Antioxidant assay

ORAC assay. The antioxidant activity of Cur and its metal complexes was performed according to Liang *et al.* [22]. Briefly, 10 µL of Cur and its metal complexes samples, prepared at (1 mg/mL), were incubated with 30 µL fluoresceine (100 nM) at 37 °C for about 10 min.



Scheme 2. Experimental design.

Metal chelation assay. This assay was performed according to Santos *et al.* [23]; 20 µL of freshly prepared $FeSO_4$ were mixed with 50 µL of Cur and Cur complexes in 96 wells plate. Then, 30 µL of ferrozine was added to each well. Then the plates were incubated at room temperature for about 10 min. The decline in the color intensity was measured at 562 nm.

DPPH assay. The antioxidant activity of Cur and its metal complexes were seeded using a DPPH free radical assay carried out according to Boly *et al.* [24]. About 100 µL of DPPH reagent was added to about 100 µL of Cur; the reaction was incubated at room temperature for about 1/2 h in the dark.

ABTS assay. The antioxidant assay was carried out according to Arnao *et al.* [25]; 192 mg of ABTS were dissolved in dist.H_2O and transferred to a 50 mL flask, then the volume was completed with dist.H_2O. 1 mL, the reaction was incubated for about 1/2 h in the dark.

Statistical analysis

Statistical analysis was done by using SPSS (version 27) software were used to analyze data followed by a post hoc test to analyze the data. ($p < 0.05$) value was considered significant.

RESULTS AND DISCUSSION

Microanalytical and conductance studies

The Cur metal complexes was subjected to elemental analysis. Carbon and hydrogen confirming that the molar reaction ratio is 1:2 (Metal:Curcumin). For the copper(II) complex, the value of magnetic measurements was found to be convenient with the geometrical formation of square-planar. The curcumin complexes structure were elucidated using infrared, electronic spectra, ^{1}H-NMR, SEM, and TEM. The molar conductance Cur metal complexes solutions of 1 x 10^{-3} mol/cm^3 in DMSO, Λ_m, were 32, 27, 28 and 33 Ω^{-1} mol^{-1} cm^{-1} for Mg(II), Ca(II), Cu(II) and Se(IV), respectively, which is very low, proving the absence of chloride ions inside or outside chelation sphere confirming non-electrolytic nature, while for Cr(III) curcumin $\Lambda_m = 45$ Ω^{-1} mol^{-1}

cm^{-1} relatively high compared to other curcumin complexes, confirming that chloride ions are inside complexation sphere [26, 27] and this was confirmed by $AgNO_3$ test.

Spectral measurements data of curcumin and curcumin metal complexes

Electronic spectra

The methanolic solution of Curcumin showed characteristic UV-Visible maximum absorption band at 425 nm. A weak absorption band appeared at 260 nm. The maximum absorption bands appeared owing to the dipole electronic allowed excitation type of π-π* due to the extended conjugation system. Where attraction takes place between (methanol, polar solvent) and polar chromophores in curcumin, methanol makes stabilization for bonding electronic ground states and the π* excited states. This interaction causes the n-π* transition to Excited state and π-π* has low energy and close n-π*[28]. While for Cur complexes: for Mg(II), at 205, 260, 425, 450 nm, for Ca(II), at 205, 255, 420, 440 nm, for Cu(II) at 205, 250 425 nm, for Cr(III), at 205, 255, 420, 440 nm and at 201 and 420 nm for Se(IV) complexes, respectively. The 1st bands at 205–300 nm due to π-π*, while bands at 300–460 nm due to n-π* [29]. Two bands appeared at 260 and 425 nm are shifted to lower and higher values, confirming the involvement of the (C=O) carbonyl group of curcumin in metal chelation.

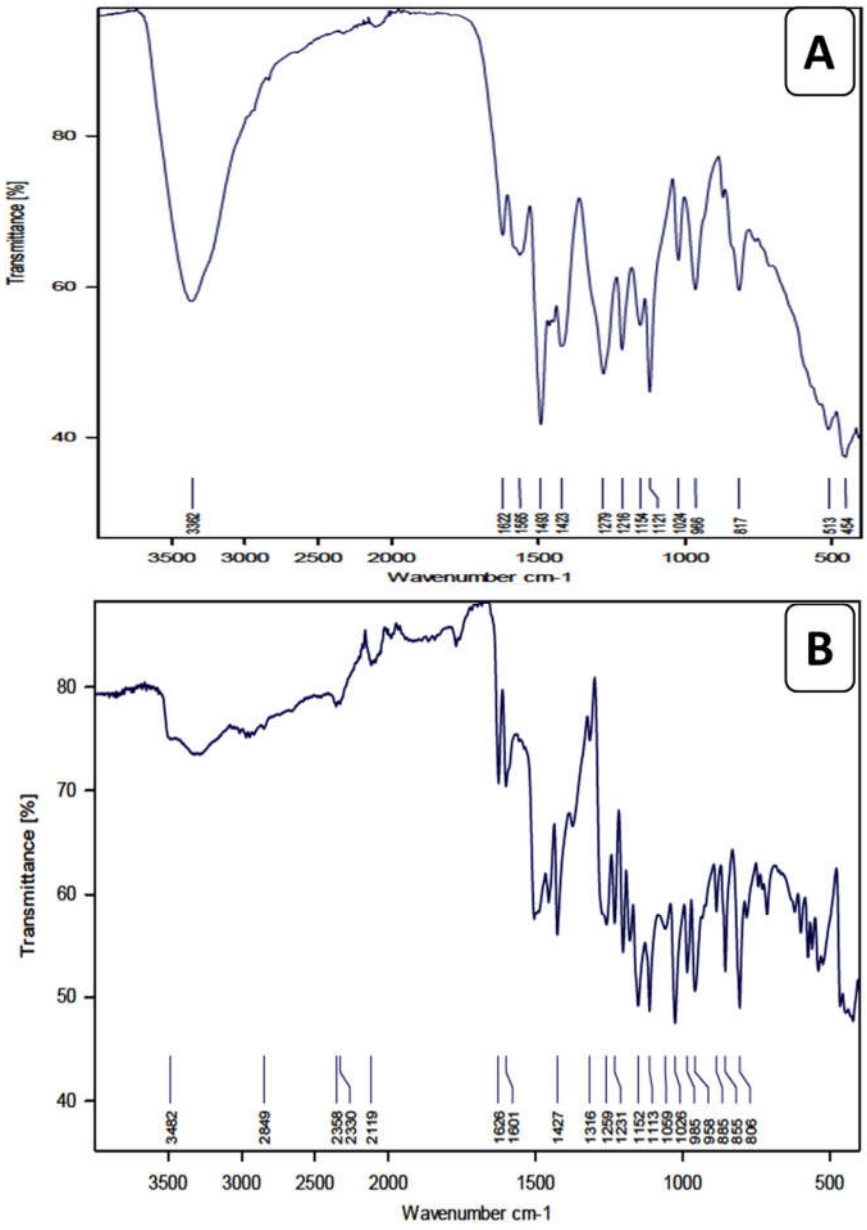
Infrared spectra

For the curcumin-free ligand, the FTIR spectrum shown in Figure 1A curcumin and Table 1 showed a band at 3500 cm^{-1} due to O-H phenolic group and vibrational motion of (C=C) aromatic appeared at 1427 cm^{-1} and for ν(C=C) aliphatic appeared at 1504 cm^{-1}. Other bands appeared at (720 and 807 cm^{-1}) assigned to the aromatic stretching vibrations of (–C=CH) [30, 31]. At 1271 cm^{-1}, an intense band appeared due to the OH phenolic group's δ (C-O) bending vibration. FTIR spectra for B) Mg(II), C) Ca(II), D) Cu(II), E) Cr(III), and F) Se(IV) curcumin chelates are so close and differ from curcumin ligands. For Cur at 1626 and 1598 cm^{-1} due to C=O are shifted to lower energy in Cur chelates [9], confirming that curcumin C=O group in enol form chelated to Mg(II), Ca(II), Cu(II), Cr(III) and tetravalent metal (Se). Also, for curcumin chelates the presence of an intense band in the range 1271-1279 cm^{-1} attributed to bending vibration δ (C-O) of the phenolic group, confirming the absence of phenolic -OH in the Cur complexes. New bands at 450–470 cm^{-1} are due to metal oxygen bands [32-35]. The bands at 3200–3500 cm^{-1} for coordinated and uncoordinated water canno be justified.

For hydrated curcumin complexes, the presence of molecules of H_2O is explained by appearance of bands at 3400 cm^{-1}, 500–600 cm^{-1} and 900 cm^{-1} due to M-H_2O [36].

Table 1. Infrared spectral bands (cm^{-1}) for Cur and their metal chelates.

Comp-ound	ν(O–H)	ν(CO) keto	ν(C=C) aliphatic	δ(CO)enol ν(C=C) aromatic	δ(CO) phenol	δ(C=CH) aliphatic	ν(M–O)
Cur	3510	1626 1598	1504	1427	1271	807 770	-
Mg(II)	3288	1626 1601	1504	1426	1259	806 712	470
Ca(II)	3362	1624 1585	1505	1423	1279	817 736	454
Cu(II)	3500 br 3370	1624 1589	1503	1428	1273	810 735	465
Cr(III)	3482 br	1626 1601	158	1427	1259	806 730	460
Se(IV)	3500 br 3319	1626 1586	1508	1425	1276	812 735	458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1121
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513
454
3500
3000
2500
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500
Wavenumber cm-1
B
Transmittance [%]
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70
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3482
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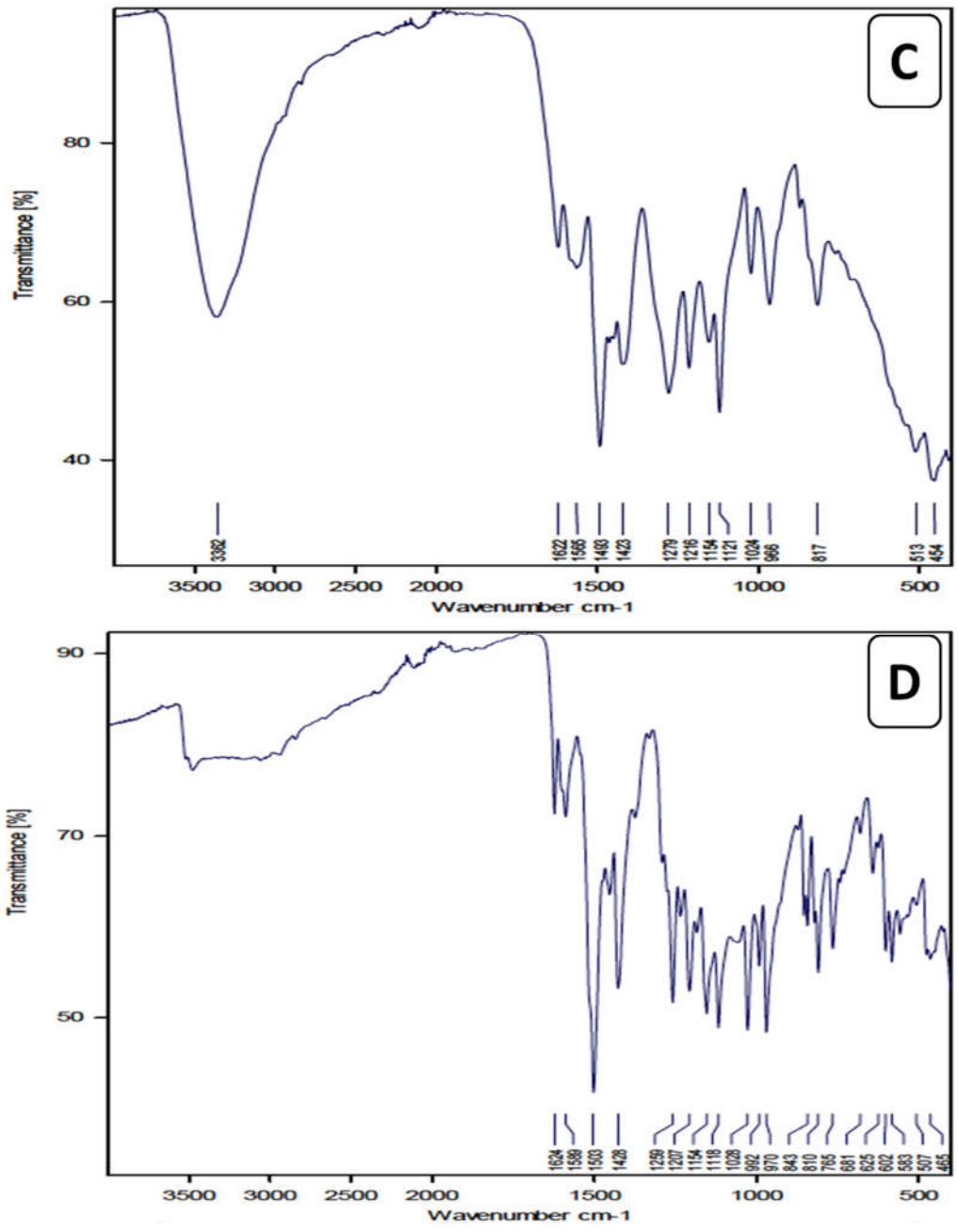
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Wavenumber cm-1
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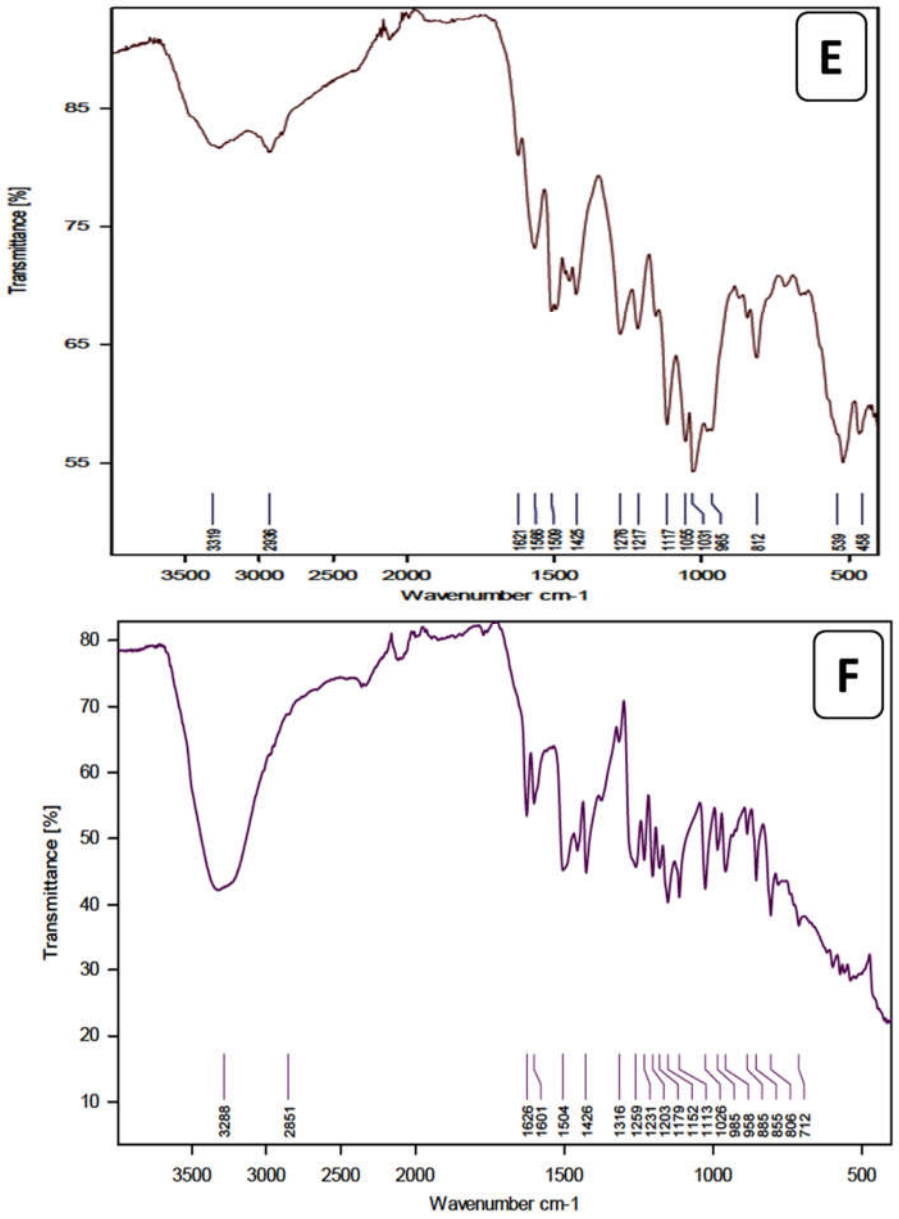

Figure 1. FT-IR of: A) curcumin, B) Mg(II)/Cur, C) Ca(II)/Cur, D) Cu(II)/Cur, E) Cr(III)/Cur and F) Se(IV)/Cur chelates.

^{1}H NMR spectra

For free curcumin ligand, the chemical shifts are: 2.51 (DMSO), δ = 3.36 (H_2O; moisture water), δ = 3.85 (3H; $AOCH_3$), d = 6.07 (1H; C1), d = 6.73 (1H; C3), d = 6.82 (1H; C9), d = 7.17 (1H; C10), d = 7.33 (1H; C6), δ = 7.59 (1H; C4), δ = 9.66 (1H; AOH phenol) and δ = 10.05 (1H; AOH enol). ^{1}H NMR spectrum of Ca(II), δ (ppm): 2.406 (DMSO), δ = 3.634 (H_2O), δ = 3.816 (3H; -OCH_3), δ = 5.570 (1H; C1), δ = 6.665 (1H; C3), δ = 6.795 (1H; C9), δ = 7.178 (1H; C10), δ = 7.245 (1H; C6), δ = 7.322 (1H; C4), δ = 9.547 (1H; -OH phenol) and δ = disappeared (1H; -OH enol). In the Ca(II) spectrum, signals due to protons of CH-diene and aromatic has been shifted. The OH signal is shifted due to (Ca-oxygen bond). The peaks at 2.00 ppm are due to moisture and do not change after chelation between calcium and curcumin [37].

Scanning electron microscopy (SEM)

The surface morphology for Cur and its metal chelates was clarified by SEM analysis Figure 2. The crystals of Cur complexes have particles that differ in shape and size. The free curcumin ligand has solid pieces with protrusions shape while the Cur chelates show the agglomeration of particles with a morphological structure and non-uniform small particle grain size.

Cur-chelates particles size increase irregularly with elongated morphology after agglomeration. The particle sizes of the Cu(II) Figure 2B and Se(IV) Figure 2C are in the diameter range of microns 0.15 µm while Ca(II) Figure 2D and Mg(II) complexes in the range of microns 0.2 µm. These particle sizes of mentioned complexes are within the range of nano-size structures.

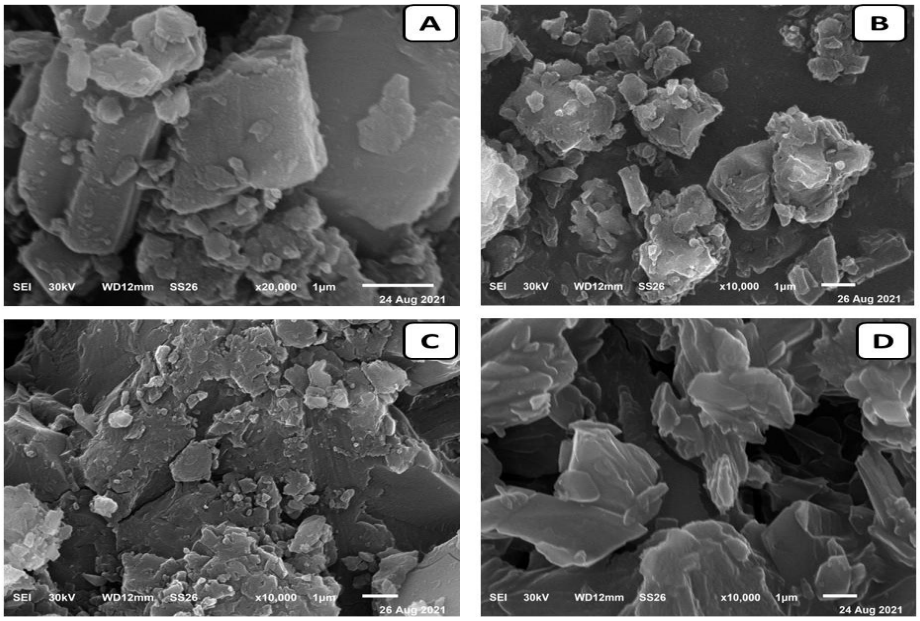

Figure 2. SEM of: A) Curcumin, B) Cu(II)/Cur, C) Se(IV)/Cur and D) Ca(II)/Cur chelates.

Transmission electron microscopy (TEM)

Figure 3 shows TEM images for synthesized divalent, trivalent, and tetravalent Se Cur complexes. The metal chelates of Cur have an orderly matrix in the pictograph confirming a homogeneous phase material for Cur complexes. The presence of spherical black spots in the metal Cur chelates with a grain size of 72.21-88.75 nm, 34.89-57.33 nm, and 80.71-100 nm for Cu(II) Figure 3B, Cr(III) Figure 3C and Se(IV) Cur Figure 3D, respectively, are observed.

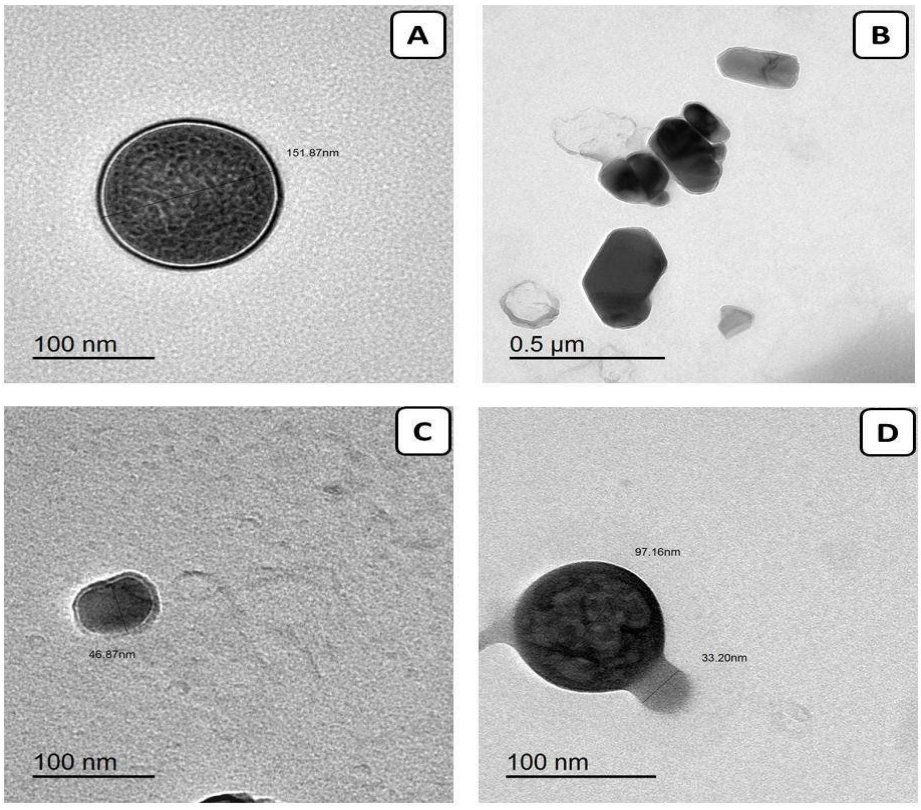

Figure 3. TEM of: A) Mg(II)/Cur, B) Cu(II)/Cur, C) Cr(III)/Cur and D) Se(IV)/Cur chelates.

X–Ray

For Cu(II) curcumin complexes, the X–ray powder diffraction patterns are shown in Figure 4. The involvement of Cu-element was confirmed using XRD. Using Deby-Scherrer formula by (FWHM) of prominent intensity for main specific peaks, the size of the complex crystallinity can be calculated [38]. Where symbol D is the size of a particle of crystal gain, K is the value of Cu grid 0.94 which is constant, and λ wavelength which is 1.5406 Å, θ is the position of the peak and β is the width of the integral peak. Based on the highest intensity value and by making a comparison with other peaks, the size particle can be calculated. According to the obtained data, the particle size is within the range of 70-90 nm.

$$D = \frac{K\,\lambda}{\beta \cos\theta} \quad (1)$$

$$\beta = \frac{\lambda}{D \cos\theta} - \varepsilon \tan\theta \quad (2)$$

$$\delta = \frac{1}{D^2} \quad (3)$$

Since the dislocation density and strain are the manifestations of the dislocation network in the complexes. The dislocation density (δ) was evaluated as Eq. 3 [39] and listed in Table 2.

Table 2. The dislocation density (δ) of Cu(II)-Cur complex.

Complex	2 θ	d value (Å)	Δ (1012.lin.m^{-2})	δ (10^{-4})
Cu(II)-curcumin	16	6	0.0201	6.1213

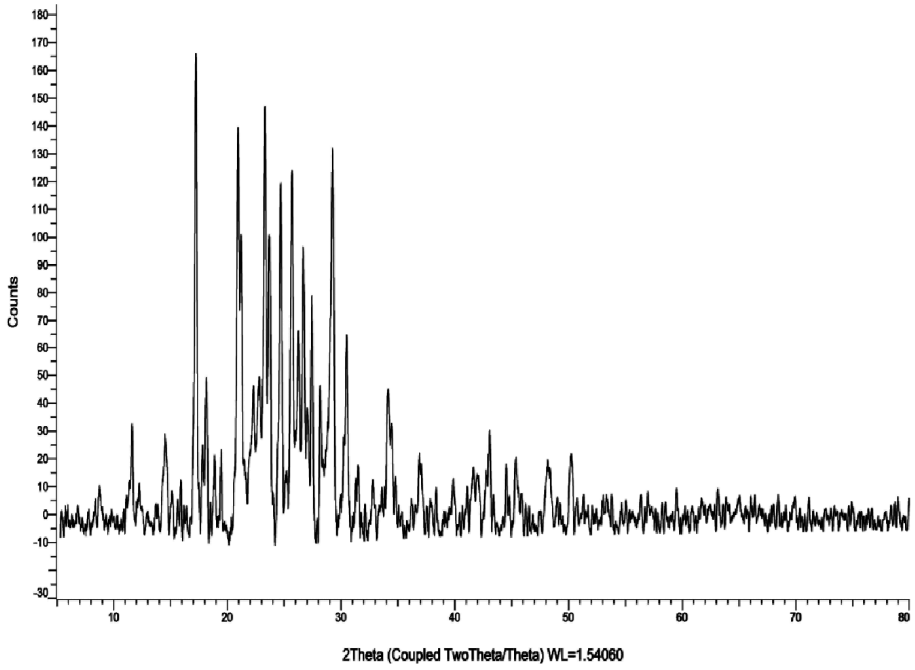

Figure 4. XRD of Cu(II)/Cur complex.

Antioxidant capacities of curcumin metal complexes

The chelating capacities were obtained using four different methods, as shown in Table 3. FRAB, metal chelation, ABTS, and DPPH methods were used. The activity of Mg/Cur, Se/Cur, Cur/Cu, Ca/Cur, and Cr/Cur complexes to scavenge the ABTS radical was higher than curcumin itself, the

same as the chelating activity of Mg/Cur and Se/Cur, Cr/Cur, and Ca/Cur were higher than Cur itself (Table 3 and Figure 5). Similarly, the highest scavenging activities were for both Se/Cur and Mg/Cur by determining the DPPH radical stability. Thus, these metal complexes with more chelating activity than Cur itself (Table 3 and Figure 5).

Table 3. Antioxidant activity of Cur and its metal complexes.

Sample name	FRAB		Metal chelation		ABTS		DPPH	
	(µM eq/mg)		(µM EDTA eq/mg)		(µM Trolox eq/mg)		(µM Trolox eq/mg)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Curcumin	6.17	0.74	6.95	0.94	135.98	11.94	18.08	0.81
Cur/Cr	1669.67	138.78	920.14	125.67	3448.05	158.85	947.19	12.54
Cur/Mg	2851.84	162.65	1399.04	90.76	4248.11	108.28	955.47	15.87
Cur/Ca	1354.55	128.97	550.49	80.97	2558.75	105.81	900.54	14.78
Cur/Cu	2085.83	142.95	750.98	102.55	2676.85	125.98	740.86	16.96
Cur/Se	1690.58	120.39	910.63	90.53	3554.58	153.28	945.25	13.58

Trolox eq: Trolox equivalents; SD: Standard deviation; *Superscript letters clarify significant differences ($p < 0.05$) between Curcumin metal complexes activities.

The FARAP capacities of the curcumin metal complexes obtained are shown in Table 3. However, in this case, Mg/Cur and Cu/Cur had the highest antioxidant activity than the antioxidant capacity of Cur itself. These results are great confirmation for the highest free radical absorbance activities of novel synthesized Cur metal complexes than Cur. This could be due to great lipophilic activity, especially of Mg/Cur as shown in (Table 3 and Figure 5).

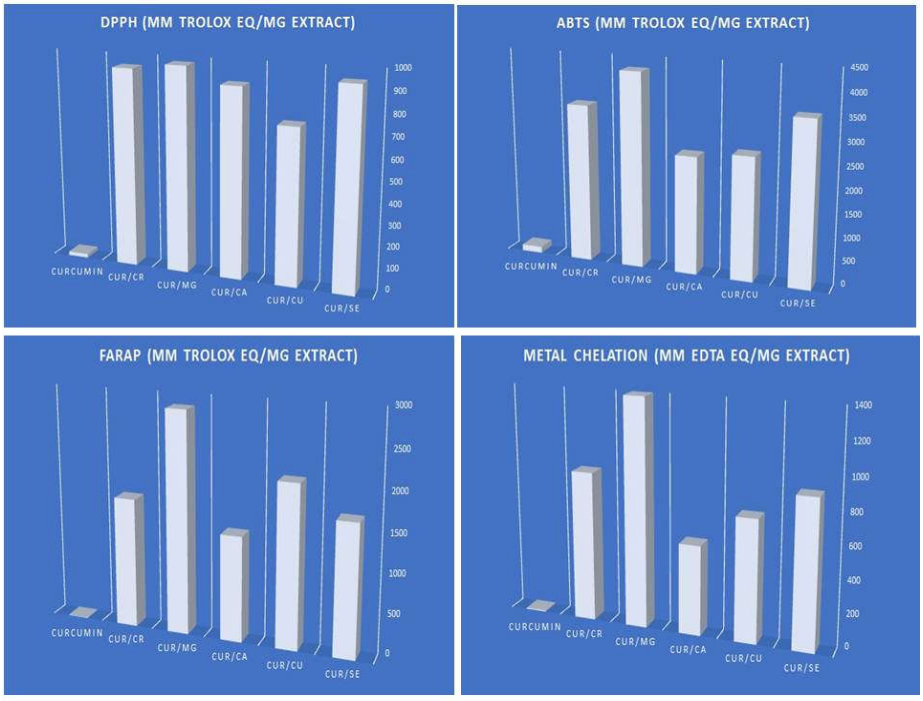

Figure 5. Antioxidant capacity of Curcumin and its metal complexes.

DISCUSSION

Lipid peroxidation is the vital mechanism involved in the incidence of major diseases such as diabetes mellitus, hepatic diseases, and cancer. Cur as an active compound in turmeric can exhibit lipid peroxidation and stabilize the cellular membranes as demonstrated previously [40].

The current results that demonstrated the high antioxidant capacities of either Cur/Se, Cur/Mg, and/or Cur/Cu are in accordance with previous results of [41], who demonstrated the percentage of DPPH inhibition for different turmeric extracts at different concentrations. An essential role in the prevention of atherosclerosis [41] and these results may open the gate for our novel complexes to be used as therapeutic agents in alleviating risky heart diseases. Additionally, the inhibitory action of Cur on lipid bioaccumulation, oxidation as well as the formation of inflammatory genes, and its stimulation can affect the therapeutic effects of Cur in the pathogenesis of hepatic and pancreatic as well as cancer diseases and even in severe cases of damage induced by tobacco smoking [41].

In accordance with the previous study of [42] who reported the remarkable potency of Cur that can relieve some of the external cancerous lesions in humans. Additionally, Cur has potential activity in treating many neuro-diseases due to potent free radical scavenging activities [43].

Additionally, supplementation of Cur has been reported to decline risk stages of systolic blood pressure in renal failure patients, cases of proteinuria, and even hematuria [44].

Additionally, our study demonstrates that our novel synthesized complexes can alleviate all these symptoms due to their high efficiency as proven as potent antioxidants with capacities that are higher than Cur itself and all these findings are in accordance with the previous study of [45] who reported highly antioxidant capacities of turmeric from some regions that may perform cellular lipid peroxidation and enhance the oxidative damages caused by excessive production of free radicals [45]

A remarkable confirmation of our obtained results that confirm the great antioxidant capacities of our novel synthesized complexes is that the medium that was used in preparation was different from the other Cur ligand and thus may add force point and antioxidant more advantage than the Cur itself, as previously reported that antioxidant capacity of Cur depends on its structure and also on the pH of the environment. Cur acts as an extraordinarily potent hydrogen-atom donor at pH 3–7. The quick release of H-ion from the Cur is very much beneficial for its antioxidant action. The release of the H- atom from the OH- of the Cur molecule is correlated directly with the free radicals quenching and reactive oxygen species. In contrast, pH above 8, the enolate form, Cur acts mainly as an electron donor, a mechanism more typical for the scavenging activity of phenolic antioxidants [45] and this confirms the current complexes in the current study that confirms the complexes between Cur and other metals and acting then as more potent antioxidants.

Additionally, the antioxidant capacity of Cur can be elevated by making essential changes in its native structure, making it an electron-rich molecule so that it can act as a better-reducing agent to reduce the concentration of excessive production of reactive oxygen molecules [46].

One exciting method involving the structural changing of Cur native structure can be to elevate the length of the hydrophobic alkoxy group attached to the benzene ring in Cur as this will make the Cur ring more electron-rich and via which the O–H bonds become weak at the phenyl ring, and this would be more acceptable to get broken easily, and that would enable an easier and quicker hydrogen-ion release. All these explanations confirm the novel antioxidant capacities of the novel synthesized Cur metal complexes.

Previous reports by Chen *et al.* suggested that Cur triggers the production of reactive oxygen species at very low concentrations and enhances reactive oxygen production [46]. A recent report by Huanga *et al.* confirmed that Cur could play antioxidative roles in neurons treated with Cu^{+2} [47]. This agrees with the current finding which confirmed the potent antioxidant capacities of the Cur/Cu complex by chemical antioxidant tests that were higher than Cur itself.

Meanwhile, Cur at low concentrations showed antioxidative activity and prooxidative activity [48]. Studies showed that cellular uptake levels of Cur are higher in tumor cells than in normal cells [48]. Additional studies show that low concentrations of Cur may protect the hepatocytes by reducing lipid peroxidation and cytochrome c release. Interestingly, GSH is the most antioxidant enzyme involved in human cells. The GSH levels in tumor cells tend to be lower than those of the normal cells, thus elevating the sensitivity of tumor cells towards Cur [49, 50].

CONCLUSION

Cur metal complexes were prepared and characterized by elemental analysis, IR, ^{1}H NMR, electronic spectra, X–ray diffraction, and SEM and TEM. The complexes were of different geometries: Octahedral and Square Planar. Our results confirmed that all curcumin–metal complexes were efficient with more antioxidant potency to alleviate oxidative injury and reactive oxygen species (ROS). Zn, Cu, Cr, and Se/Cur complexes showed potent antioxidant activities. These results open a new gate for developing therapeutic strategies for treating degenerative diseases that could be alleviated by potent and highly active antioxidants such as Cur metal complexes that were synthesized in the current study and may potentially be shared in the prevention of oxidative stress complications.

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REFERENCES

1. Majid, S.J.; Taha, M.R.; Uday, M.N.; Salim, A.; AlMalki, F.A.; Albaqami, J.; AlYamani, A.A.; Taqi, Z.J.; Ghassan, M.S. Inhibition of *Staphylococcus aureus* α-hemolysin production using nanocurcumin capped Au@ZnO nanocomposite. *Bioinorg. Chem. Appl.* **2022**, 2022, 2663812.
2. Ngwabebhoh, F.A.; Erdagi, S.I.; Yildiz, U. Pickering emulsions stabilized nanocellulosic-based nanoparticles for coumarin and curcumin nanoencapsulations: In vitro release, anticancer and antimicrobial activities. *Carbohydr. Polym.* **2018**, 201, 317–328.
3. Dhule, S.S.; Penfornis, P.; Frazier, T.; Ryan, W.; Joshua, F.; Grace, T.; Jibao, H.; Alina, A.; Vijay, J.; Radhika, P. Curcumin-loaded c-cyclodextrin liposomal nanoparticles as delivery vehicles for osteosarcoma. *Nanomed. Nanotechnol. Biol. Med.* **2012**, 8, 440–451.
4. Hany, M.A.; Ali, M.A.; Khalaf, M.M.; Aly, A. New iron(III), cobalt(II), nickel(II), copper(II), zinc(II) mixed-ligand complexes: Synthesis, structural, DFT, molecular docking and antimicrobial analysis. *Bull. Chem. Soc. Ethiop.* **2024**, 38, 147–166.
5. Hasan, H.A.; Mahdi, S.M.; Ali, H.A. Tetradentate AZO Schiff base Ni(II), Pd(II) and Pt(II) complexes: Synthesis, spectral properties, antibacterial activity. Cytotoxicity and docking studies. *Bull. Chem. Soc. Ethiop*. **2024**, 38, 99–111.
6. Wu, Y.; Yang, Y.; Zhang, Z.; Wang, Z.; Zhao, Y.; Sun, L. A facile method to prepare size-tunable silver nanoparticles and its antibacterial mechanism. *Adv Powder Technol.* **2018**, 29, 407–415.
7. Tanvir, E.M.; Sakib, H.; Fuad, H.; Rizwana, A.; Siew, H.G.; Ibrahim, K.; Nurul, K. Antioxidant properties of popular turmeric (*Curcuma longa*) varieties from Bangladesh. *J.Food Qual*. **2017**, 2017, 8471785.
8. Al-Salmi, F.A.; El-Megharbel, S.M.; Hamza, R.Z. Synthesis and spectroscopic study of novel mixed ligand formula "Artemisinin/Zn" and assessment of its inhibitory effect against "SARS-CoV-2″. *Heliyon* **2023**, 9, e17177.

9. Shasha, D. Reversed phase HPLC-UV quantitation of BHA, BHT and TBHQ in food items sold in Bindura Supermarkets, Zimbabwe. *Int. Res. J. Pure Appl. Chem.* **2014**, 4, 578–584.
10. Afroz, R.; Tanvir, E.; Zheng, W.; Little, P. Molecular pharmacology of honey. *J. Clin. Exp. Pharmacol.* **2016**, 6, 1000212.
11. Hamza, R.Z.; Alsolami, K. Ameliorative effects of orlistat and metformin either alone or in combination on liver functions, structure, immunoreactivity and antioxidant enzymes in experimentally induced obesity in male rats. *Heliyon* **2023**, 9, e18724.
12. Parth, M.; Tapan, K.M. Structure-function elucidation of antioxidative and prooxidative activities of the polyphenolic compound curcumin. *Chin. J. Biol.* **2014**, 2014, 396708.
13. Shen, Y.; Han, C.; Chen, X.; Hou, X.; Long, Z. Simultaneous determination of three curcuminoids in curcuma by liquid chromatography-tandem mass spectrometry combined with pressurized liquid extraction. *J. Pharm. Biomed. Anal.* **2013**, 81-82, 146–150.
14. Anand, P.; Thomas, S.G.; Kunnumakkara, A.B.; Chitra, S.; Kuzhuvelil, B.H.; Bokyung, S.; Sheeja, T.T.; Krishna, M.; Indira, P.; Kallikat, R.; Bharat, A. Biological activities of curcumin and its analogues (congeners) made by man and mother nature. *Biochem. Pharmacol.* **2008**, 76, 1590–1611.
15. Sharma, O.P. Antioxidant activity of curcumin and related compounds. *Biochem. Pharmacol.* **1976**, 25, 1811–1812.
16. Qahl, S.; Hamza, R. Quercetin ameliorates hepatic structure and function, alleviate testicular damage and mitigate oxidative stress induced by monosodium glutamate in male rats. *Egy. J. Vet. Sci*. **2024**, 55, 585–597.
17. Mishra, S.; Kapoor, N.; Ali, A.M.; Pardhasaradhi, B.V.V.; Kumari, A.L.; Ashok. K.; Krishna, M. Differential apoptotic and redox regulatory activities of curcumin and its derivatives. *Free Radic. Biol. Med.* **2005**, 38, 1353–1360.
18. Kunwar, A.; Barik, A.; Sandur, S.K.; Priyadarsini, I.K. Differential antioxidant/pro-oxidant activity of dimethoxycurcumin, a synthetic analogue of curcumin. *Free Radic. Res.* **2011**, 45, 959–965.
19. Rice-Evans, C.A.; Miller, N.J.; Paganga, G. Antioxidant properties of phenolic compounds. *Trends. Plant Sci*. **1997**, 2, 152–159.
20. AlBasher, G.; Mohamed, M.A.; Almeer, R.; Khairy, A.I.; Hamza, R.Z.; Bungau, S.; Aleya, L. Synergistic antioxidant effects of resveratrol and curcumin against fipronil-triggered oxidative damage in male albino rats. *Environ. Sci. Pollut. Res.* **2020**, 27, 6505–6514.
21. Abu-El-Zahab, H.S.H.; Hamza, R.Z.; Al-Ahmed, J.A. Ameliorative effect of vitamin C and curcumin on malathion induced hepatorenal toxicity in male mice. *J. Chem. Pharm. Res.* **2016**, 8, 990–999.
22. Liang, Z.; Cheng, L.; Zhong, G.Y.; Liu, R.H. Antioxidant and antiproliferative activities of twenty-four vitis vinifera grapes. *PLoS One* **2014**, 9, e105146.
23. Santos, J.S.; Brizola, V.R.A.; Granato, D. High-throughput assay comparison and standardization for metal chelating capacity screening: A proposal and application. *Food Chem*. **2017**, 214, 515–522.
24. Boly, R.; Lamkami, T.; Lompo, M.; Dubois, J.; Guissou, I. DPPH free radical scavenging activity of two extracts from *Agelanthus sosoneifolius* (Loranthaceae) Leaves. *Int. J. Toxicol. Pharmacol. Res.* **2016**, 8, 29–34.
25. Arnao, M.B.; Cano, A.; Acosta, M. The hydrophilic and lipophilic contribution of total antioxidant activity. *Food Chem*. **2001**, 73, 239–244.
26. El-Megharbel, S.M.; Hamza, R.Z. Synthesis, spectroscopic characterizations, conductometric titration and investigation of potent antioxidant activities of gallic acid complexes with Ca(II), Cu(II), Zn(III), Cr(III) and Se(IV) metal ions. *J. Mol. Liq.* **2022**, 358, 119196.
27. Alexandru, T.B.; Cyril, P.; Ion, G.C.; Jean-Jacues, A.; Zuzana, Z.; Omar, R.M. Curcumin–benzodioxaborole chelates. *ARKIVOC* **2005**, XIII, 1- 9.

28. Christian, G.D.; O'Reilly, J.E. *Ultraviolet and Visible Absorption Spectroscopy in Instrumental Analysis*, 2nd ed.., Allyn and Bacon Publisher: Boston; **1986**.
29. Al-Thubaiti, E.H. Antibacterial and antioxidant activities of curcumin/Zn metal complex with its chemical characterization and spectroscopic studies. *Heliyon* **2023**, 9, e17468.
30. Sambhu, N.D. Relativistic quantum chemistry and rigorous variational analysis. *Proc. Indian Acad. Sci. (Chem. Sci.)* **1994**, 106, 445-466.
31. Bellamy, L.J. *The Infrared Spectra of Complex Molecules*, 3rd ed., Chapman and Hall: London; **1975**.
32. Song, Y.M.; Xu, J.P.; Ding, L.; Hou, Q.; Liu, J.W.; Zhu, Z.L. Syntheses, characterization and biological activities of rare earth metal complexes with curcumin and 1,10-phenanthroline-5,6-dione. *J. Inorg. Biochem.* **2009**, 103, 396.
33. Socrates, G. *Infrared Characteristic Group Frequencies*, 1st ed., John Wiley and Sons: New York; **1980**.
34. Nakamoto, K. *Infrared and Raman Spectra of Inorganic and Coordination Compound*, Wiley: New York; **1978**.
35. Patel, G.P.; Sharma, S.S.; Vora, J.J.; Joshi, J.D. Synthesis and characterization of nickel(II), cadmium(II) and zinc(II) mixed ligand complexes with 2,2'-bipyridylamine and phenol. *Synth. React. Inorg. Met. Org. Chem.* **2002**, 32, 792.
36. Barik, A.; Mishra, B.; Kunar, A.; Kadam, R.M.; Dutta, S.S.L.; Padhye, S.; Satapati, A.K.; Zhang, H.Y.; Priyadarsini, K.I. Comparative study of copper(II)-curcumin complexes as superoxide dismutase mimics and free radical scavengers. *Eur. J. Med. Chem.* **2007**, 42, 431.
37. Zhao, X.Z.; Jiang, T.; Wang, L.; Yang, H.; Zhang, S.; Zhou, P. Interaction of curcumin with Zn(II) and Cu(II) ions based on experiment and theoretical calculation. *J. Mol. Struct.* **2010**, 984, 316.
38. Quan, C.X.; Bin, L.H.; Bang, G.G. Mater. Preparation of nanometer crystalline TiO_2 with high photo-catalytic activity by pyrolysis of titanyl organic compounds and photo-catalytic mechanism. *Chem. Phys.* **2005**, 91, 317–324.
39. Velumani, S.; Mathew, X.; Sebastian, P.J. Structural and optical characterization of hot wall deposited CdSe*x*Te1−*x* films. *Sol. Energy Mater. Sol. Cells* **2003**, 76, 359.
40. Malik, P.; Mukherjee, T.K. Structure-function elucidation of antioxidative and prooxidative activities of the polyphenolic compound curcumin. *Chin. J. Biol*. **2014**, 2014, 396708.
41. Bengmark, S.; Mesa, M.D.; Gil, A. Plant-derived health: The effects of turmeric and curcuminoids. *Nutr. Hosp*. **2009**, 24, 273–281.
42. Kuttan, R.; Sudheeran, P.C.; Josph, C.D. Turmeric and curcumin as topical agents in cancer therapy. *Tumori*. **1987**, 73, 29–31.
43. Mishra, S.; Palanivelu, K. The effect of curcumin (turmeric) on Alzheimer's disease: An overview. *Ann. Indian Acad. Neurol*. **2008**, 11, 13–19.
44. Khajehdehi, P.; Zanjaninejad, B.; Aflaki, E.; Mohamadali, N.; Fariborz, A.; Malekmakan, L.; Gholam-Reza, D. Oral supplementation of turmeric decreases proteinuria, hematuria, and systolic blood pressure in patients suffering from relapsing or refractory lupus nephritis: A randomized and placebocontrolled study. *J. Renal Nutr*. **2012**, 22, 50–57.
45. Widowati, W.; Sardjono, C.T.; Wijaya, L.; Laksmitawati, D.R.; Darsono, L. Free radicals scavenging activities of spices and curcumin. Proceedings of the Second International Syposium on Temulawak and the 40th Meeting of National Working Group on Indonesian Medicinal Plant, **2011**.
46. Chen, J.; Da, W.; Zhang, D.; Liu, Q.; Kang, J. Water-soluble antioxidants improve the antioxidant and anticancer activity of low concentrations of curcumin in human leukemia cells. *Pharmazie* **2005**, 60, 57–61.
47. Huanga, H.C.; Lin, C.J.; Liu, W.J.; Jiang, R.R.; Jiang, Z.F. Dual effects of curcumin on neuronal oxidative stress in the presence of Cu(II). *Food Chem. Toxicol.* **2011**, 49, 1578–1583.

48. Kunwar, A.; Barik, A.; Sandur, S.K.; Priyadarsini, I.K. Differential antioxidant/pro-oxidant activity of dimethoxycurcumin, a synthetic analogue of curcumin. *Free Radic. Res.* **2011**, 45, 959–965.
49. Syng-Ai, C.; Kumari, A.L.; Khar, A. Effect of curcumin on normal and tumor cells: Role of glutathione and BCL-2. *Mol. Cancer Ther.* **2004**, 3, 1101–1108.
50. Ghoneim, A.I. Effects of curcumin on ethanol-induced hepatocyte necrosis and apoptosis: Implication of lipid peroxidation and cytochrome C. *Naunyn-Schmiedeberg's Arch. Pharmacol*. **2009**, 379, 47–60.