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Research Article

Enhancing the Solubility of Curcumin Metal Complexes and Investigating Some of Their Biological Activities

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This article describes the synthesis of curcumin complexes with metal ions. Properties of these complexes such as spectra IR and UV-Vis and solubility were investigated. The optimum parameters of ultrasound to enhance the solubility was figured out as follows: the capacity of ultrasound: 750 W/g; the time of ultrasound: 7 min; the concentration of the surfactant Tween 80 : 2%. The maximum solubility (mg/ml) of complexes was as follows: Cur-Fe(III): 0.162 ± 0.01; Cur-Zn(II): 0.267 ± 0.02; and Cur-Ca(II): 0.417 ± 0.05. Antioxidant capacity (DPPH, %I) of curcumin complexes was higher than that of curcumin-free complexes. All of these curcumin complexes revealed antimicrobial activities, in which calcium complex had the best resistance against *Salmonella*, followed by Fe(III) complexes. Meanwhile, the zinc complex was not resistant to this bacterium. These complexes showed antibacterial activity on *Staphylococcus aureus*, in which Cur-Ca (II) complexes had the highest antibacterial activity. For *Escherichia coli*, the Cur-Zn (II) complex had no resistance, while the Cur-Ca (II) complex showed the highest antibacterial activity.

1. Introduction

Recently, curcumin complexes with metal ions have attracted the attention of researchers around the world. Curcumin complexes have different properties compared to a free form of curcumin: due to the presence of ketone functional groups linked to metal ions, the complex molecule is more stable, and so it has better bioavailability. In curcumin metal complexes, not only the chemical and physical properties of curcumin but also the bioactivity of the metal ions has been changed. The toxicity of metal ions could be reduced when complexes were formed. Curcumin is a ligand, and thus it forms stable complexes with almost all the metal ions and nonmetals. In general, stable structures with 1 : 1, 2 : 1 (ligand : metal) stoichiometry are observed [1]. According to Khalil et al., a 3 : 1 (ligand : metal) complex of curcumin with Fe^{3+} was synthesized [2]. The 1 : 1 curcumin-Al^{3+} complex showed less affinity to DNA binding than free Al^{3+}, which has been attributed to its ability to reduce the development of Al^{3+}-induced Alzheimer's disease [3]. Baum and Ng reported that copper and iron react with curcumin to form complexes which suggest one possible mechanism of action in Alzheimer's disease animal models [4]. Five coordinated curcumin-$Au3^{+}$ complexes were synthesized and investigated antiarthritic activity in vivo by Sharma et al. [5]. Curcumin also degrades the toxicity of heavy metals like Hg^{2+}, Cd^{2+}, and Pb^{2+}. Heavy metal-induced oxidative stress was reduced through complex formation [6–11]. Due to binding progress, the curcumin-metal complexes generate DNA damage and thereby exhibit pro-oxidant behavior. Curcumin-metal complexes are also being discovered as better antitumor agents than curcumin itself [12, 13]. Mei et al. synthesized a new zinc(II)-curcumin complex and studied the effects of antidepressants in rodent models of gastric ulcer and depression induced by stresses [14]. Neuroprotective effects and mechanisms of curcumin-Cu(II) and curcumin-Zn(II) complexes systems and their pharmacological implications were reported by Yan et al. [15]. In another interesting study of Banerjee, mononuclear complexes of curcumin with Cu(II) and Zn(II) have been synthesized and characterized and their effects on the fibrillization and aggregation of amyloid-beta (Aβ) peptide

have been studied [16]. Iwunze has prepared and characterized the Cr-curcumin complex by differential pulse voltammetry and UV-Vis spectrophotometry [17]. An overview report of Priyadarsini showed the great importance of curcumin as well as its derivatives and complexes [18].

Today, almost all metal curcumin complexes are being studied in biology and pharmaceuticals. Notably, there has been impressive increase of relevant contributions to this field in recent times. Although there have been many studies on the complexes of curcumin with metal ions, the low solubility of these complexes makes it difficult to apply in cosmetics, functional foods, and the pharmaceutical industry. Therefore, the study of how to increase the solubility of these complexes is necessary to extend their applicability. In this work, we have synthesized 3 complexes of curcumin and metal ions (Cur-Fe(III), Cur-Zn(II), and Cur-Ca(II)) and studied their solubility with the support of surfactants and ultrasound.

2. Materials and Methods

2.1. Chemicals and Equipment. All used chemicals and solvents were in analytical grade and were used without further purification unless otherwise mentioned. Double distilled and degasified water was used in this study. Ethanol 96°(v/v), acetone, ethyl acetate, DPPH (2,2-diphenyl-1-picrylhydrazyl), trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid), curcumin, and silica gel were purchased from Sigma-Aldrich Pvt. Ltd.

Yamato RE301 vacuum rotary evaporator, VCX 750 ultrasound system, UV-Vis spectrometer, Thermo Genesys 10S UV-Vis, and HLPC/MS Agilent 1260 with UV-Agilent probe have been used in this research.

2.2. Quantitative Analysis Method. The curcumin content and its complexes were analyzed by the UV-Vis method at 424 nm and by the HPLC-UV method.

2.3. IR and MS Spectra. The IR of curcumin complexes was recorded on the FTIR-8400S-SHIMADZU spectrometer using KBr pellets. The MS spectra were recorded on a Bruker micro-TOF-Q 10187 spectrometer.

2.4. Preparation of Curcumin Complex. Metal chloride salt was mechanically mixed in a mortar with curcumin (metal ion: curcumin 1 : 1 mol with Ca^{2+} and Zn^{2+}; 1 : 3 with Fe^{3+}) until homogenous powder mixtures were obtained. Then, propylene glycol/water (1 : 1 v/v) solution was added to the mixtures followed by mechanical shaking at 25°C until pasty combinations appear. The combinations then were dried at 60°C to obtain powdered complexes of curcumin metal ion. These complexes were purified by silica gel column chromatography G60.

2.5. Determination of Solubility of Curcumin-Metal Complexes. The above refined curcumin complex weighed 0.1 g (m_1) and was placed in a 50 ml measuring cylinder, 2 ml Tween 80 was added, then water was added up to the mark, and an ultrasound was performed at different capacities. The mixture was centrifuged at a speed of 5000 rpm for 15 minutes. After that, the mixture was filtered through a filter paper to collect residue that was washed in ethanol. The residue was dried at 60°C to constant mass and weighed again (m_2). The solubility was calculated according to the following formula:

$$\text{solubility (mg/ml)} = \frac{(m_1 - m_2) * 1000}{50}. \quad (1)$$

2.6. Morphology of Curcumin Complex Solution. The morphology of curcumin complexes in solution was observed by transmission electron microscope (TEM; JEM 1400, JEOL, Japan). About 10 μL of the sample was dropped in the specimen place and covered by a 400 mesh grid. After 1 minute, 10 μL of uranyl acetate was dropped on top of the grid, and this sample was allowed to dry for 30 minutes before being observed under the electron microscope. This procedure was used to confirm the particle size in the solution.

2.7. Determination of Antioxidant Capacity by DPPH. The antioxidant activity of curcumin complexes was determined by DPPH radical scavenging by UV spectroscopy.

2.8. Study on the Antimicrobial Activity of Curcumin Metal Ion Complexes. *E. coli*, *S. aureus*, and *Salmonella* were grown in Müeller–Hinton broth (MHB). Equal volumes (100 μL) of the bacterial culture suspensions (107 CFU/mL) were added to Petri dish containing TSA. All samples were incubated for 24 h at 37°C. Amoxicillin was used as a standard antibacterial agent. Stock solutions of antimicrobial agents were prepared at a concentration of 5 mg/mL (w/v). DMSO was utilized to dissolve the complex solutions and antimicrobial agents.

The agar plate was divided into equal parts, and then 100 μl of bacteria (reached OD value of 0.1 at 610 nm) was taken and transplanted evenly on the plate. Then, 10 μl of the curcumin-ion metal complex solution was added to a 6 mm diameter filter paper on a bacterial agar plate. 10 μl DMSO and amoxicillin were also carried out similar to curcumin-ion metal complexes solution. After being incubated at 37°C for 24 hours, antibacterial ring diameter was measured.

2.9. Data Analysis. All data are presented as average ± standard deviation (SD). All data for evaluations were obtained in triplicate ($n = 3$). Statistical analyses used in this study were unpaired Student's t-test and one-way ANOVA. Significant statistical differences were shown on the values of $p < 0.05$.

3. Results and Discussion

3.1. Efficiency of Formation Complex. The efficiency of the formation complex is described in Figure 1, in which the efficiency of the curcumin complex with Fe (III) was the highest (97.5%), followed by curcumin-Zn (II) (66.5%) and curcumin-Ca (II) complex (39.5%). Figure 2 indicates that the obtained

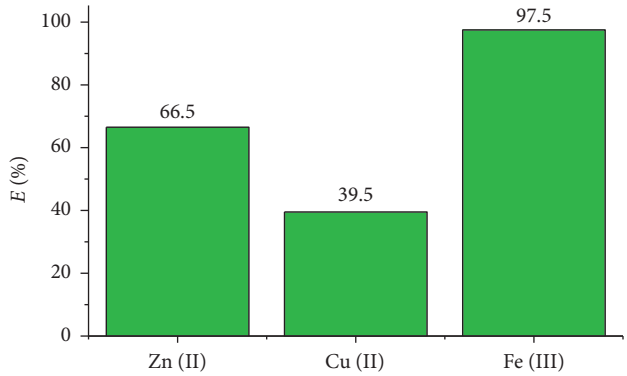
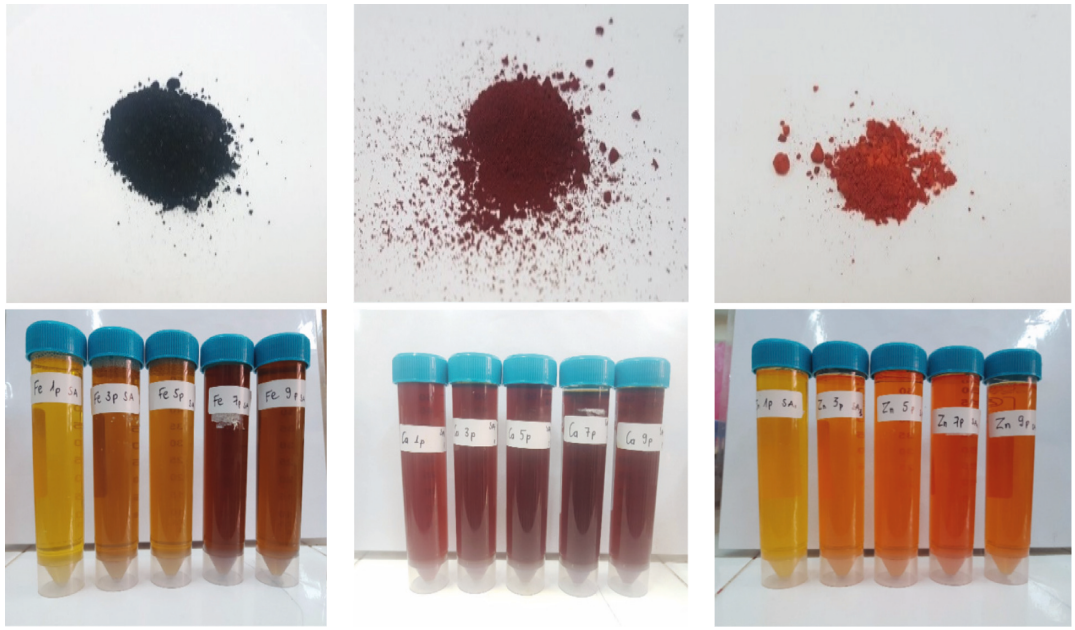


Figure 1: The efficiency of formation complexes.



(a) (b) (c)

Figure 2: The complexes of curcumin-metal ion (above solid, under solution): (a) curcumin-Fe(III), (b) curcumin-Ca(II), and (c) curcumin-Zn(II).

complexes have characteristic colors from black to orange. This result is also quite consistent with the previous studies [19].

3.2. Spectra of Complexes. The absorption spectra of the curcumin and its complexes under the optimum conditions are shown in Figure 3. In this figure, the spectra of Cur and their complexes were shown, respectively, against ethanol blank. As an observation, the maximum absorption peak of the Cur lies at 424 nm, corresponding π to π^* transition of the -C=O- bond, which was in accordance with the typical spectra as observed by another worker. Whereas, the absorption peak of the complexes was located at 432 nm (Cur-Cu (II)), 500 nm (Cur-Fe(III)), and 428 nm (Cur-Zn(II)).

The infrared spectrum of CUR and its complexes were investigated. From the results shown in Table 1, the structure of curcumin was confirmed by the appearance of a weak band within the range 3500 cm^{-1} corresponding to -OH. The FT-IR spectra also showed a weak band or shoulder located at 3051 cm^{-1} which was assigned to aromatic C-H. The oscillation of the group C=O was confirmed by the frequency at stretching vibration at 1605 cm^{-1}. Compared with the reference spectrum of curcumin, all complexes showed a great decrease in the intensity of the (C=O) carbonyl band. Besides, a net decrease in the intensity of the free (OH) hydroxyl group of curcumin was observed in the case of curcumin complexes. These above phenomena indicated that metal ions interacted with functional groups.

3.3. Effect of Tween Concentration on Solubility. The results from Table 2 and Figure 4 show how Tween 80 concentration

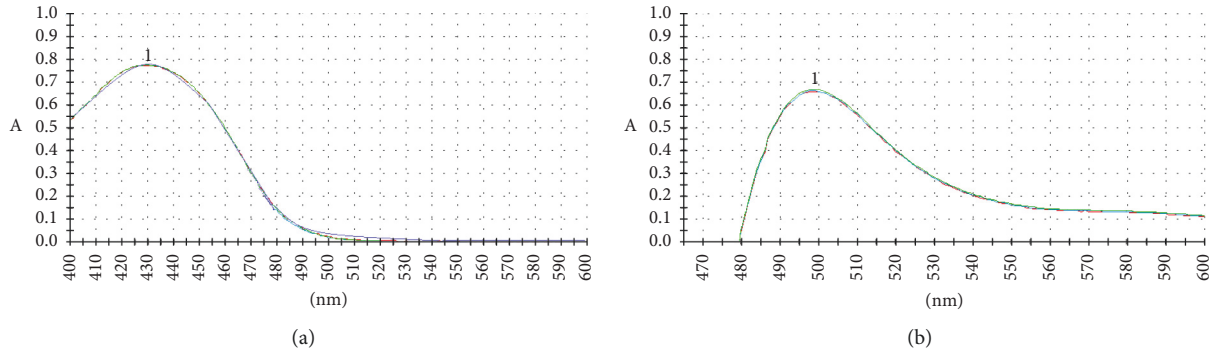


Figure 3: Absorption spectra of the Cur-Zn(II) (a) and Cur-Fe(III) (b).

Table 1: The frequency of functional groups in curcumin and its complex in the IR spectrum.

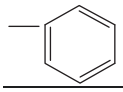
Groups	Curcumin (cm^{-1})	Cur-Ca(II) (cm^{-1})	Cur-Fe(III) (cm^{-1})	Cur-Zn(II) (cm^{-1})
–OH	3500.67	—	—	3532.40
–C=O	1626.35	1589.17	1619.85	1624.09
–C=C–	1601.87	1557.49	1589.05	1594.06
–C–O–C–	1113.59	1124.27	1121.05	1120.57
	2970.78	2971.65	2988.17	2942.10
	1505.77	1479.60	1486.93	1491.92
	1455.92	1448.65	1447.31	1451.02

Table 2: Solubility of curcumin metal complex in water solvent at different Tween concentrations.

Conc. of Tween 80 (%w/v)	Solubility (mg/ml)		
	Cur-Fe(III)	Cur-Ca(II)	Cur-Zn(II)
0.1	$(0.0660 \pm 0.004)^{k}$	$(0.2180 \pm 0.004)^{d}$	$(0.0596 \pm 0.002)^{k}$
0.5	$(0.0777 \pm 0.004)^{j}$	$(0.2851 \pm 0.007)^{c}$	$(0.0876 \pm 0.003)^{i}$
1	$(0.0862 \pm 0.002)^{i}$	$(0.2991 \pm 0.003)^{b}$	$(0.1209 \pm 0.003)^{g}$
1.5	$(0.0898 \pm 0.001)^{i}$	$(0.3027 \pm 0.002)^{b}$	$(0.1473 \pm 0.006)^{f}$
2	$(0.1058 \pm 0.002)^{h}$	$(0.3278 \pm 0.007)^{a}$	$(0.1989 \pm 0.004)^{e}$
2.5	$(0.1064 \pm 0.008)^{h}$	$(0.3293 \pm 0.008)^{a}$	$(0.2004 \pm 0.003)^{e}$

In the same column, different values indicate differences according to the columns ($p < 0.05$).

affects the solubility of curcumin complexes. The solubility of complexes tended to increase steadily when the concentration of Tween 80 increased from 0.1% to 2%. There was no significant difference in solubility of complexes when Tween concentrations of 2% and 2.5% were dissolved. At the concentration of 2% Tween 80, the solubility of curcumin complexes was as follows: Cur-Fe complexes (III): 0.1058 mg/ml; Cur-Ca complexes (II): 0.3278 mg/ml; and Cur-Zn complexes (II): 0.1989 mg/ml. This could be explained as follows: the surfactant Tween 80 surrounded individual components and prevented the fusion of these complexes. During the ultrasound process, the intermolecular bonds in the complexes will be cut into smaller sized components after which the Tween surfactant will create a shell that covers the outer particles to help stabilize the structure and increase the separation time of the system. Therefore, when the concentration increased, Tween 80 will hinder the reuniting of individual components that were severed by complexes. However, Tween 80 was only able to hinder the merging of individual components without participating in breaking links. Therefore, when the concentration of Tween 80

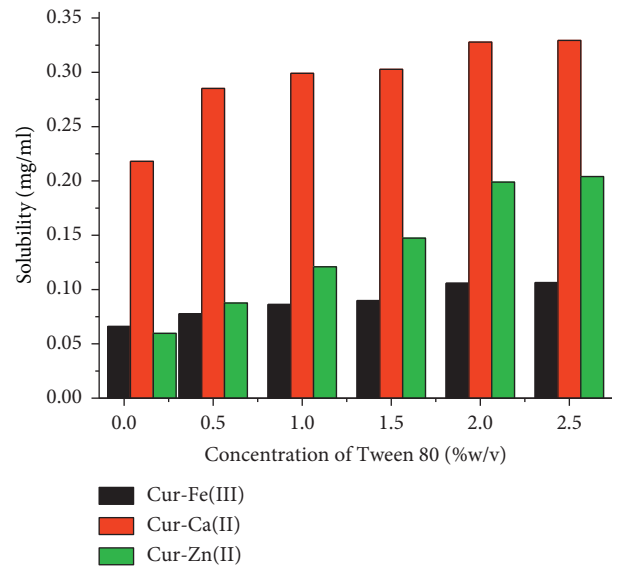


Figure 4: The effect of Tween concentration on the solubility of curcumin metal complex.

exceeded the "saturation" level, it did not affect the solubility of the compound.

3.4. Effect of the Ultrasound Capacity on Solubility. The results in Table 3 and Figure 5 indicate that the solubility of Cur-Fe (III), Cur-Ca (II), and Cur-Zn (II) complexes increased when ultrasonic capacity raised from 150 W to 750 W. The solubility of complexes was stable at ultrasonic power of 600 W: Cur-Fe (III) 0.1280 mg/ml, Cur-Ca (II) 0.3760 mg/ml, and Cur-Zn (II) 0.2298 mg/ml.

The increasing solubility of curcumin metal complexes under an ultrasound wave could be explained as follows: when ultrasound waves transmitted into the liquid environment, continuous pull and compression cycles were formed. In the compression cycle, the molecules were closer together and in the pull cycle, and they were separated. The negative pressure in the pull cycle was strong enough to overcome the forces that bonded the molecules and formed small bubbles. Air bubbles, including stable air bubbles and temporary air bubbles, became the nucleus of gas invasion. After thousands of cycles, they increased in size. Next, the ultrasound vibrated these bubbles and created the phenomenon of "shock waves." Air bubbles varying in size were broken and formed very high temperatures, pressures, and fast speeds very quickly, only through a few cycles. The greater the pressure generated, the higher the ability to break down the bonds in the complex molecule, leading to increased solubility of the complexes.

According to Li and Fogler, the reason could be explained that low-frequency (20–100 kHz) ultrasound waves exert a strong effect on the surface that divides between the two phases, making it unstable leading to the explosion of dispersed phase (oil phase) in continuous phase (water phase); in addition, the air bubbles (cavitation) in the liquid environment (gas invasion) through each cycle (−) and cycle (+) appear. At that time, the dispersed particles in the continuous phase are increasingly divided into the smallest [20]. However, when the capacity increased to 750 w/g, the solubility of the complexes did not change significantly. This proved that the solubility reached a saturation value. This could be explained by the high ultrasonic power for a certain period; the "cavitation" bubble explosion reaches the critical and saturated point. The emitted ultrasonic energy (Bjerknes energy) is increased to push the emulsion particles to enter junctions and collide with each other to recreate larger sized particles according to Pangu and Feke in 2004 [21]. Therefore, the capacity of 600 w/g was selected for subsequent experiments.

3.5. Influence of the Time of Ultrasound to Solubility. Results in Table 4 and Figure 6 show how ultrasonic time affects the solubility of Cur-ion metal complexes. The solubility of complexes gradually increased as the ultrasonic time increased. It reached the maximum at 7 minutes, then decreased again. The solubility of metal Cur-ion complexes at 7 minutes was as follows: Cur-Fe (III): 0.1618 mg/ml, Cur-Ca (II): 0.4167 mg/ml, and Cur-Zn(II) 0.2664 mg/ml.

Table 3: Solubility of curcumin complexes in water solvent at different ultrasound wave capacities.

Capacity (w/g)	Solubility (mg/ml)		
	Cur-Fe(III)	Cur-Ca(II)	Cur-Zn(II)
150	$(0.0764 \pm 0.001)^{i}$	$(0.3069 \pm 0.007)^{d}$	$(0.1236 \pm 0.005)^{g}$
300	$(0.1022 \pm 0.003)^{h}$	$(0.3278 \pm 0.010)^{c}$	$(0.1969 \pm 0.001)^{f}$
450	$(0.1082 \pm 0.002)^{h}$	$(0.3409 \pm 0.006)^{b}$	$(0.2022 \pm 0.003)^{f}$
600	$(0.1280 \pm 0.002)^{g}$	$(0.3760 \pm 0.005)^{a}$	$(0.2298 \pm 0.006)^{e}$
750	$(0.1211 \pm 0.002)^{g}$	$(0.3407 \pm 0.006)^{b}$	$(0.2207 \pm 0.002)^{e}$

In the same column, different values indicate differences according to the columns ($p < 0.05$).

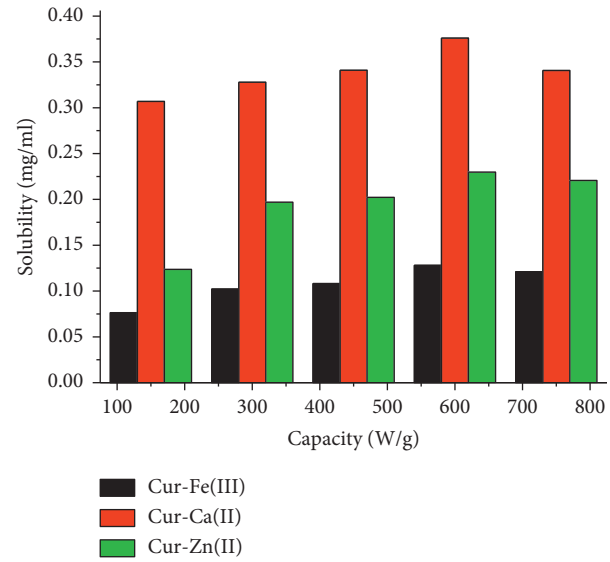


Figure 5: The effect of ultrasonic capacity on the dissolution of the curcumin metal complex.

Table 4: Solubility of the complex in the water at different ultrasound wave times.

Times (min)	Solubility (mg/ml)		
	Cur-Fe(III)	Cur-Ca(II)	Cur-Zn(II)
1	$(0.0709 \pm 0.002)^{l}$	$(0.2387 \pm 0.005)^{f}$	$(0.1862 \pm 0.007)^{h}$
3	$(0.1047 \pm 0.004)^{k}$	$(0.2583 \pm 0.006)^{d}$	$(0.1880 \pm 0.005)^{h}$
5	$(0.1253 \pm 0.001)^{j}$	$(0.3713 \pm 0.003)^{c}$	$(0.2302 \pm 0.004)^{g}$
7	$(0.1618 \pm 0.002)^{i}$	$(0.4167 \pm 0.006)^{a}$	$(0.2664 \pm 0.006)^{d}$
9	$(0.1302 \pm 0.005)^{j}$	$(0.3796 \pm 0.001)^{b}$	$(0.2484 \pm 0.002)^{e}$

In the same column, different values indicate differences according to the columns ($p < 0.05$).

The dependence of solubility on ultrasound time could be explained as follows: the longer the ultrasound time took, the more bubbles and the pull-compression cycle were formed, so the ability to break down the intermolecular was higher. In the process of breaking down air bubbles, the temperature generated around the particle was very high. The free radicals were more formed at high temperature that interacted with a previously dissolved complex to form a new complex and causes the reduction of the complexes solubility. The difference in solubility of

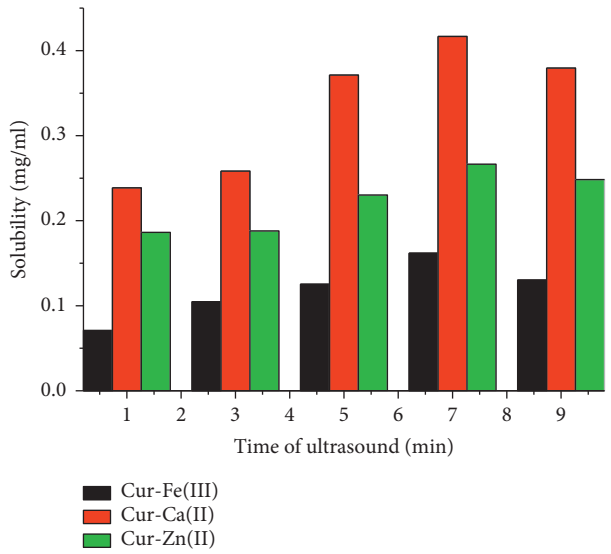


Figure 6: The effect of ultrasonic wave time on the dissolution of curcumin metal complexes.

complexes could be explained through the stability of complexes. For Cur-Ca (II) complex, this element does not contain orbital d so the bond between the ligand and metal ion was formed from the electrostatic suction force, so the complex is the least stable. Meanwhile, Zn belongs to group IIB and this ion has orbital d, easy to form coordination bonds. In particular, Cur-Fe (III) complex with a ratio of 1 : 3 has been very stable, so it had the lowest solubility.

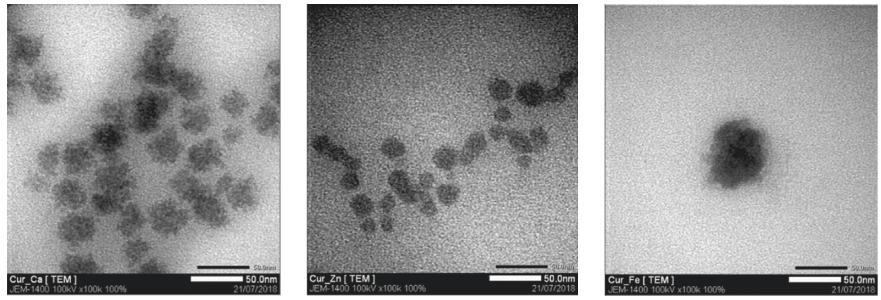
3.6. Transmission Electron Microscopy (TEM) of Complex Solution. The morphology of the curcumin complex solution analyzed using transmission electron microscopy (TEM) is depicted in Figure 7. Observation of nanoemulsion by TEM imaging was likely the best method to research specimen's morphology, purity, and particle size distribution in nonsolid disperse systems. As being presented in Figure 7, the spherical droplets were monodispersed with uniform particle size to demonstrate the formation of complex particles with metal ions, ranging in size from 20–50 nm.

3.7. Antioxidant Activity. The results in Figure 8 indicate that calcium-curcumin complex showed the highest antioxidant capacity, followed by zinc and iron complexes. The antioxidant capacity of these 3 complexes was all higher than the capacity of free curcumin.

The antioxidant capacity of complexes was higher than free curcumin because free curcumin molecules could be easily oxidized by other agents and changed the structure. Barik et al. concluded that the Cur-Cu(II) complex would be able to undergo and sustain the distortion from square-planar geometry to the distorted tetrahedral one during its reaction with superoxide radical. This allows for the compound to remain intact and undergo many redox cycles and hence act as a very efficient antioxidant. These findings clearly emphasize the need for further synthetic studies and the fine-tuning of the biological activities of metal curcumin complexes through ligand variations [22]. The other scientists reported that the antioxidant activities of curcumin complexes with Zn(II), Cu(II), Fe(II), Mg(II), and Mn(II)) have better DPPH radical scavenging and ferrous reducing power activities than free curcumin with the same dosage [23].

3.8. Antimicrobial Activity. The antimicrobial activity of curcumin complexes on *Salmonella*, *Staphylococcus aureus*, and *Escherichia coli* was investigated. In this experiment, positive control samples were amoxicillin and negative control samples were DMSO. The results in Figure 9 show that Cur-Ca (II) had the best resistance to *Salmonella*, followed by the Cur-Fe (III) complex. Meanwhile, Cur-Zn (II) complex was not resistant to this bacterium. All metal ion curcumin complexes showed antibacterial activity on *Staphylococcus aureus*, in which Cur-Ca (II) complex had the highest antibacterial activity with an antibacterial ring diameter of 19.75 mm, followed by Cur-Zn (II) complex: 4.50 mm and Cur-Fe (III) complex: 2.25 mm. The resistance of *Escherichia coli* of all 3 complexes was lower than that of the two bacteria above. The Cur-Ca(II) complex had the highest antibacterial ring diameter of 3.25 mm.

Compared to the results of Bagchi et al. [24], who studied the antibacterial ability of 1 : 1 Fe-Cur complex, the results of 1 : 3 Fe-Cur complexes in this project showed higher antibacterial ability. A high concentration of curcumin in the complex may have a higher antimicrobial effect. Meanwhile, the antibacterial ability of free metal and free curcumin was not higher than that of their complexes. This could be explained that complex curcumin released more slowly than the free form, so the possibility of oxidation was slower. So, the antibacterial activity of the complexes was higher than that of free curcumin. According to Refat [25], metal curcumin complexes showed "multi-anti" so the ability of



(a) (b) (c)

Figure 7: Transmission electron microscopy (TEM) analysis of curcumin complexes. (a) Cur-Ca(II); (b) Cur-Zn(II); (c) Cur-Fe(III).

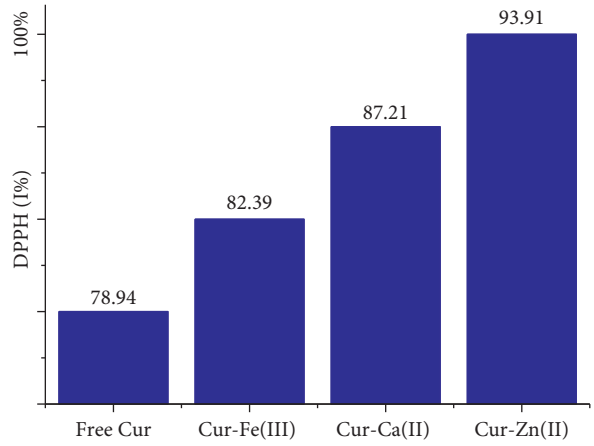


Figure 8: Antioxidant capacity (%) of curcumin complexes and free curcumin at the concentration of 100 μg/ml.

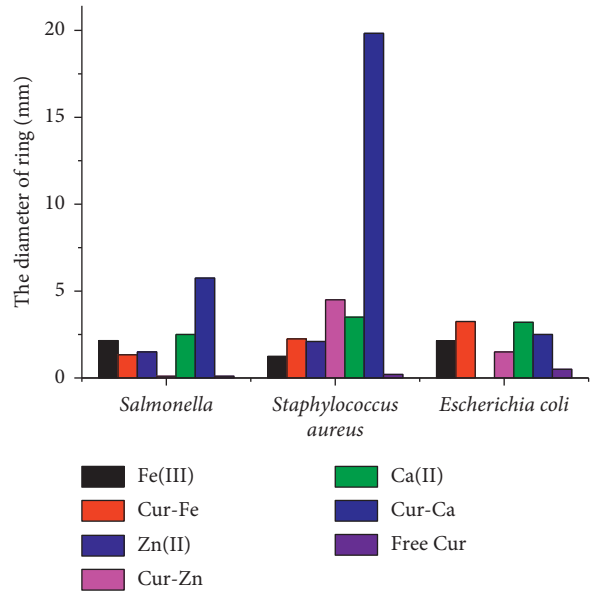


Figure 9: Antimicrobial activity of curcumin metal ion complexes and free curcumin at the concentration of 100 μg/ml.

antioxidant and antimicrobial activities of complexes were better than those of free curcumin and free metal ions. The high antibacterial of the Cur-Ca (II) complex is remarkable. Therefore, this complex will be further studied to be applicable in practice.

4. Conclusions

The curcumin complexes with metal ions were synthesized and their solubility was investigated in water with the aid of ultrasonic waves. Their solubility increased hundreds of times compared to the control samples. These complexes also showed better antioxidant activity than the free form of curcumin. Their antimicrobial activity was also investigated, and the results showed that these complexes had antibacterial properties on the investigated bacterial strains. In the next work, we will prepare the nanoemulsion of these complexes to increase their applicability.

Data Availability

All data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

The authors have contributed equally to this work.

Acknowledgments

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