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ACTIVITY OF Zn(II)-CURCUMIN COMPLEX COMPOUND AS AN ANTIBACTERIAL AGENT AGAINST *Staphylococcus aureus* AND *Escherichia coli*

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Abstract

Curcumin has very broad biological activities, but it has low stability. The stability of curcumin can be enhanced by forming complex compounds with metal ions, hoping to preserve its activity. This paper reports the antibacterial activity of zinc(II)-curcumin compared with curcumin alone. Zinc(II)-curcumin complexes have been prepared using $ZnCl_2$ metal precursor in ethanol under reflux conditions with a curcumin:metal molar ratio of 2:1. The reaction, followed by thin-layer chromatography, showed that curcumin had reacted completely with zinc(II) metal ions after 4 hours of reaction. The UV-vis spectra of the Zn(II)-Curcumin complex experienced a bathochromic peak shift of 5 nm. The FTIR spectra of the zinc(II)-curcumin complex indicated interactions between the *β*-1,3 diketone groups of curcumin and Zn^{2+} metal ions, manifested by a decrease in absorption band intensity and shift in wave numbers of phenolic -OH and enolic C=O groups. Antibacterial activities of curcumin and zinc(II)-curcumin were evaluated using the disc diffusion method against *E.coli* and *S.aureus* bacteria. Curcumin and zinc(II)-curcumin exhibited a moderate antibacterial activity against the bacteria. Inhibition zone diameters against *E.coli* demonstrated by curcumin and zinc(II)-curcumin at a dose of 100 µg/disc are 6.05 mm and 5.30 mm, respectively. Meanwhile, at the same dose, curcumin and zinc(II)-curcumin showed inhibition zone diameters against *S. aureus* in 5.39 mm and 6.09 mm, respectively. The observations demonstrate the preservation of curcumin's antibacterial activities although it is introduced with zinc(II) ion.

INTRODUCTION

Curcumin is the main natural polyphenol found in the rhizome of turmeric (*Curcuma longa)*. Curcumin has long been used traditionally as a medical herb and has been shown to exhibit activity up to the cellular level [1]. Based on the analysis of curcumin structure, it was shown that functional groups such as *β*-diketone groups, phenolic hydroxy and double bonds in the middle chain could potentially have an effect on the biological activity of curcumin [2]. Some of the biological activities of curcumin include as an anti-inflammatory, antioxidant, antiviral, antiparasitic, and antinociceptive while curcumin has also been utilized as a therapeutic ingredient for neurodegenerative diseases [3], [4], [5], [6]. In addition, curcumin also has antibacterial activity against both gram-positive and gram-negative bacteria [7]. However, curcumin has a major weakness that prevents its widespread use, where curcumin is unstable, this occurs as a result of the *β*-diketone group in curcumin that is susceptible to hydrolysis [8]. The stability of curcumin compounds will be destabilized by light, heat, solvents and air. This instability of curcumin causes poor bioavailability or cellular absorption, where the molecule undergoes a short metabolism and elimination in the body [1]. Prasad *et al.* [8] reported that curcumin incorporated with metals improves the stability of the curcumin and increases the effectiveness of the biological activity of curcumin.

Peni *et al.* [9] reported that curcumin-metal complexes can be synthesized with Na^{+}, Mg^{2+} and Cu^{2+} ions which is confirmed through the FTIR spectroscopy. The spectra of the metalated curcumin show the change in the absorption band and the shift in the vibration wavenumbers, specifically the –OH bond in the phenolic group, the C=O, carbonyl functional group and the appearance of the M-O (M= metal) absorption band. Kareem *et al.* [10] also prepared curcumin metal complexes with Co^{2+}, Ni^{2+} and Cu^{2+} ions and

it has been reported that curcumin metal complexes exhibit better antibacterial activity compared to free curcumin.

One of the metals that can be used to increase the biological activity of curcumin is zinc metal. It was reported that zinc metal shows biological activity and is directly involved in the catalysis and co-catalysis of enzymes that control many cellular processes including DNA synthesis [11]. Zinc metal is in the group of transition metals which in its second oxidation number (Zn^{2+}) can potentially bind ligands well to form complex compounds. In addition, zinc metal also has a fairly high electronegativity value (1.6) in which the greater the electronegativity value of the metal, the resulting complex tends to be more stable because the metal's ability to attract electron pairs donated by the ligand will also be stronger [12].

Several studies have proven the activity of zinc(II) complex compounds that bind to ligands, show better results as antibacterial. Lely *et al.* [13] prepared a complex of sulfamethoxazole with zinc(II) ion, reported that the antibacterial activity of the sulfamethoxazole-Zn(II) complex was better compared to sulfamethoxazole itself. In addition, Vimalraj *et al.* [14] has also successfully synthesized a zinc(II) complex with a silibinin (sil) ligand to form $[Zn(sil)(H_2O)_2]$ which shows significantly good inhibitory activity of *Escherichia* coli (gram-negative) and *Staphylococcus aureus* (gram-positive) bacteria.

Therefore, in this study, curcumin will be reacted with zinc(II) ion to form the complex of zinc(II)-curcumin. The complex was then examined for antibacterial activity against *Escherichia* coli as a representative of gram-negative bacteria and *Staphylococcus aureus* as a representative of gram-positive bacteria. The test was carried out by using the disc diffusion method.

EXPERIMENT

Material

The materials used in this study were *Staphylococcus aureus* and *Escherichia* coli bacteria, dichloromethane (CH_2Cl_2; Merck), ethanol (C_2H_5OH; Merck), disc paper (Macherey Nagel), curcumin ($C_{12}H_{20}O_6$), methanol (CH_3OH; Avantor), sodium hydroxide (NaOH; Merck), nutrient agar (NA) (Merck), nutrient broth (NB) (Merck), thin-layer chromatography plate (TLC) (Merck), tetracycline, zinc chloride ($ZnCl_2$; Merck).

Instrumentation

The instruments used in this study were analytical balance (Ohaus), autoclave (All American), FTIR (Prestige-21 Shimadzu), laminar air flow (SZ Air Tech), shaker incubator (Sartorius) and UV-Vis Spectrophotometer (Shimadzu 1280).

Procedure

Synthesis of Zn(II)-Curcumin Complex

The synthesis of the Zn(II)-curcumin complex was carried out referring to our previous report [9]. The complex compound Zn(II)-curcumin was prepared by reacting the $ZnCl_2$ salt and curcumin at a molar ratio of 1 to 2 (1:2). Curcumin (200 mg, 0.54 mmol) was dissolved in 30 mL of ethanol until dissolved. Sodium hydroxide solids (21.72 mg, 0.54 mmol) were then added to the curcumin solution. After that, the $ZnCl_2$ (36.92 mg, 0.27 mmol) that had been dissolved in 1 mL of ethanol was added drop-by-drop into the mixture while stirring and heating. The mixture was then heated while stirring under reflux in ethanol for 4 hours.

The reaction was followed by the thin-layer chromatography (TLC) method at 0-, 30-, 60-, 120, 180- and 240-minutes using dichloromethane: methanol eluent in a ratio of (19:1 v/v). The reaction product was then isolated by using the solvent extraction method in DCM/water solvents. The product was obtained from the dichloromethane layer, then the solvent was evaporated in a rotary evaporator to gain solid. The product was characterized by using UV-Vis and FTIR spectrophotometers.

Antibacterial Activity Test

The antibacterial activity test was carried out refers to a previous literature [15], using the disc diffusion method. The nutrient broth (NB) media (20 mL) was poured into a sterile petri dish and allowed to solidify. The bacterial inoculum that was prepared previously was spread on the surface of the medium so that it was evenly distributed. The solution of curcumin and Zn(II)-curcumin complex compounds (both compounds were dissolved in ethanol, 20 µL) were each dripped on a disc paper. The doses of the two samples used were varied, such as 100.0; 50.0, 25.0 and 12.5 µg/disc while the procedures were carried out in triple. The solution of tetracycline (1 µg/mL) (positive control) and ethanol (negative control) were also prepared and

tested along with the compounds. Incubation was carried out for 24 hours at a temperature of 37 °C. Compounds that have antibacterial activity are characterized by the formation of an inhibitory zone around the isolation area. The diameter of the formed resistance zone is measured using a caliper.

RESULT AND DISCUSSION

Synthesis of Zn(II)-Curcumin Complex

In the synthesis of this complex compound, curcumin acts as a bidentate ligand and the Zn^{2+} as the central atom. The metal precursor used is zinc chloride ($ZnCl_2$). Ethanol was utilized as the solvent because it well-dissolves curcumin and the metal precursors, in addition to its donor number that is smaller than the coordinated ligands so that the possibility of the position of the ligand being replaced by the solvent can be avoided. The synthesis process of Zn(II)-curcumin complex compounds was carried out through a reflux process as it can keep the synthesis process of complex compounds maintained.

There are three positions of oxygen atoms in the structure of curcumin ligands that potentially bind to metal ions, namely in the *β*-ketone group and in the phenolic methoxy located at both ends of the aromatic ring. However, the Zn^{2+} metal ion is more likely to bind to oxygen atoms in the *β*-ketone group, this is because the *β*-ketone group in curcumin is a strong chelating agent, so it can form bonds with the Zn metal ion as the central atom. In addition, the metal-curcumin coordination with a ratio of 1:2 results in steric repulsion in the phenolic methoxy, which will reduce the possibility of oxygen atoms at that position to bind to the metal ion [9]. **Figure 1** shows the prediction of the reaction between curcumin and zinc(II) metal ions.

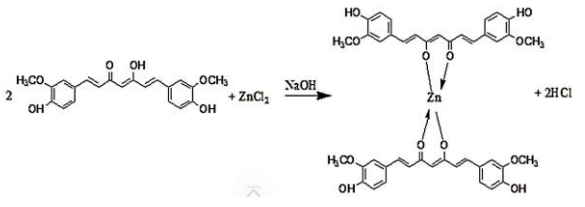

Figure 1. Prediction of the reaction between zinc(II) ion with curcumin ligand.

The reaction of curcumin and $ZnCl_2$ was followed by thin-layer chromatography (TLC). The principle of TLC is the separation of samples based on the polarity properties of the sample and the eluent in which the sample will move up following a more polar phase of motion, because the absorption of the stationary phase in each compound is different, the compound moves according to its polarity properties and therefore separation occurs. The TLC observation was done on a silica gel as a stationary phase and a moving phase (eluent) of the mixture of dichloromethane and methanol (19:1 v/v). After 4 hours reaction, the chromatogram showed 3 spots thus the isolation proceeded through a solvent extraction using DCM and water mixture.

The extraction forms 2 layers of colored solution that do not mix with each other. The upper layer of solution is reddish-orange which is the water fraction, while the lower layer is yellow which is the dichloromethane fraction. The extraction process was followed by TLC where the product is in the dichloromethane fraction which showed 1 spot with an Rf value of 0.87. Solvent extraction was carried out to remove the remaining Zn(II) metal ions and curcumin ligands.

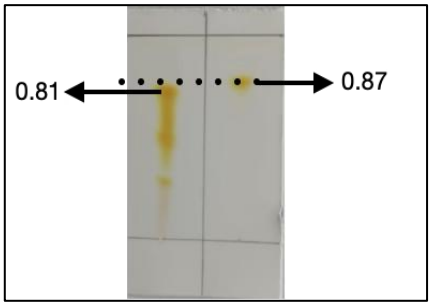

Figure 2. Thin-layer chromatogram of curcumin (left) and zinc(II)-curcumin (right).

The TLC results (**Figure 2**) showed that curcumin has an Rf value of 0.81 and the Zn(II)-curcumin at 0.87 indicates the introduction of the zinc(II) ion into curcumin. In addition, the change in the Rf value of the curcumin compound and the Zn(II)-curcumin complex shows the polarity properties difference between the two compounds. The Zn(II)-curcumin complex has a higher Rf value compared to curcumin, implying that the Zn(II)-curcumin complex is more distributed in the polar phase of motion compared to curcumin.

The Zn(II)-curcumin complex and curcumin were characterized using a UV-Vis spectrophotometer in the wavelength range of 200-800 nm with a solution concentration of $5x10^{-5}$ M. The curcumin spectrum (**Figure 3**) shows an absorption peak at a maximum wavelength of 420 nm, proposed to be due to the presence of electronic dipoles, which allows for π-π* transitions to occur [16]. The peak on the spectrum of the Zn(II)-curcumin complex has shifted towards a longer wavelength of 425 nm or bathochromic compared

to curcumin (**Figure 3**). The charge transfer that may occur in the Zn(II)-curcumin is the transfer of charge from ligand to ligand (LLCT). The transfer of LLCT charges on the Zn(II)-curcumin complex can occur between the π_{2p} orbital to the empty π_{2p}* orbital of the CO group on the curcumin ligand [17].

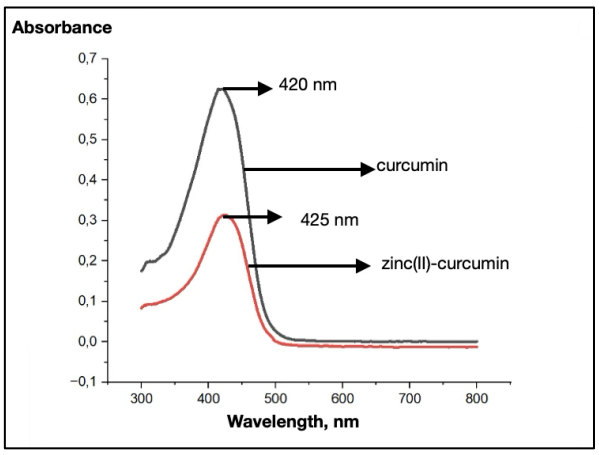

Figure 3. The UV-Vis spectra of curcumin and Zn(II)-curcumin complex.

Characterization of curcumin compounds and Zn(II)-curcumin complexes was also carried out using FTIR measured at wavelengths of 4000-400 cm^{-1}. The FTIR spectrum of curcumin (**Figure 4**) shows the existence of characteristic functional groups; the wavenumbers as well as the pattern as reported earlier by Peni *et al.* [9].

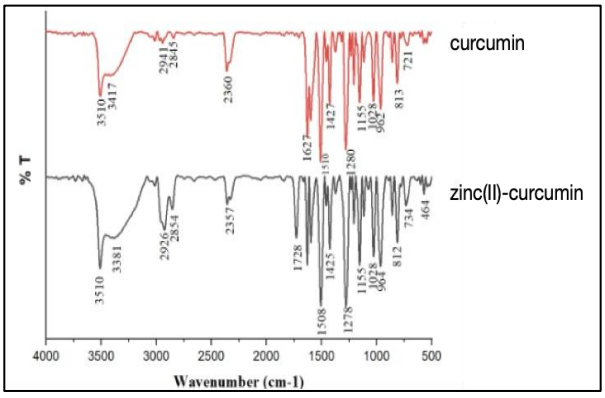

Figure 4. The FTIR spectra of curcumin and Zn(II)-curcumin complex.

The FTIR spectrum of the Zn(II)-curcumin complex (**Figure 4**) shows several differences with the curcumin spectrum, namely the shift in the number of waves and the change in intensity and peak shape. The stretching vibration of -OH in the Zn(II)-curcumin complex underwent a shift in the wavenumber to be shorter to 3381.21 cm^{-1}, in addition to a wider band shape. The phenolic -OH vibrational absorption band in compounds containing the enol group in *ß*-1,3-diketon depends on intramolecular and intermolecular hydrogen bonds. The hydroxy (-OH) and methoxy (-OCH_3) groups in phenols are accounted to cause stronger hydrogen bonds, in which the stronger the hydrogen bonds, the wider the absorption band. Thus, if these groups bind to other groups, the -OH bond in the phenol will weaken and the vibration band will shift towards the smaller wavenumber.

A new peak that is strong and sharp, assigned for C=O bond of the carbonyl functional group appears at 1728.22 cm^{-1} on the Zn(II)-curcumin spectrum, strongly indicating the complexation of curcumin in the *ß*-1,3 diketone system. The IR spectrum of zinc(II)-curcumin complex also shows a metal oxide, M-O group vibration absorption band at 464 cm^{-1} assigned for Zn-O bond. The M-O vibration in the metal-curcumin complex is generally in the range of 454 - 470 cm^{-1} wavenumber [18].

Antibacterial Activity Test

The antibacterial activity test of curcumin compounds and Zn(II)-curcumin complexes was carried out using the disc diffusion method. The disc diffusion method is one of the most common procedures, used for antibacterial examination. This method is carried out using disc paper as a medium to absorb antibacterial compounds and attached to agar media that has been inoculated with bacteria in which the samples will diffuse into the agar medium [19]. The antibacterial activity test of curcumin compounds and Zn(II)-curcumin complexes was done on *E.coli* and *S.aureus* bacteria using 4 dose variations, such as 100.0; 50.0; 25.0 and 12.5 µg/disc. The concentration variation aims to determine the difference in the inhibitory zone formed, where the higher the concentration, the larger the inhibitory zone formed [20].

The results of the antibacterial activity test of curcumin and Zn(II)-curcumin showed the growth inhibitions against *E. coli* and *S. aureus* bacteria, identified from the formation of a clear zone around the disc paper (**Figure 5**). The inhibition ability against bacteria forms a clear zone, which is then measured using a caliper. The data is depicted in **Table 1**.

Based on the data (**Table 1**), both curcumin and Zn(II)-curcumin compounds show that there is an effect of concentration on inhibition in both test bacteria, where the increasing concentration of the sample, the diameter of the inhibition formed is

also larger. Curcumin at the dose of 100.0 µg/disc showed a moderate inhibition while at doses of 50.0, 25.0 and 12.5 µg/disc demonstrated a weak inhibition against *E.*coli and *S.aureus* bacteria. The Zn(II)-curcumin complex also shows a moderate inhibition at a dose of 100 µg/disc against *E.* coli bacteria, while against *S. aureus* bacteria, the complex exhibits a moderate inhibition at doses of 100 and 50 µg/disc. Thus, the results of the antibacterial activity test show that both curcumin and Zn(II)-curcumin compounds demonstrate similar activity categorized as a moderate antibacterial. Antibacterial activity where zone of inhibition less than 5 mm is classified as weak, 5-10 mm is moderate, 11-20 mm is strong and greater than 20 mm is categorized as very strong [21].

Positive control is included to confirm the bacterial growth response and as a comparison of effectiveness between the standard antibacterial and the samples by comparing the diameter of the formed inhibition zone [22]. Tetracycline and ethanol were used as positive and negative controls, respectively. Tetracycline is one of the antibiotics that can inhibit the synthesis of bacterial proteins, both gram-positive and gram-negative bacteria. Meanwhile, the negative control functions to determine whether there is an influence of solvents on the bacterial inhibition, so that it can be ascertained that the inhibition zone formed comes from the test compound and not from the solvent used negatively [23].

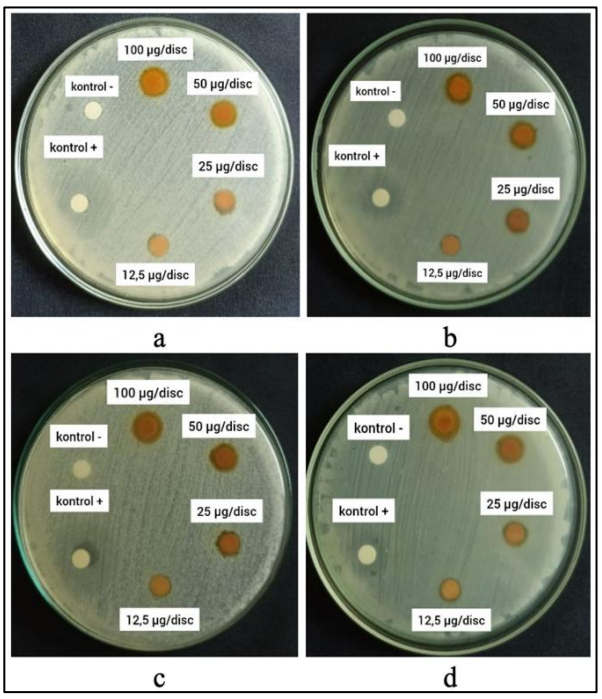

Figure 5. Curcumin inhibitory zones against *bacteria (a) E.coli* and *(b) S.aureus*, Zn(II)-curcumin inhibitory zones against bacteria (c *) E.coli,* and (d) *S.aureus.*

Table 1. Antibacterial Activity Test Results of Curcumin and Zn(II)-curcumin Complex Against *E.coli* and *S.aureus* Bacteria.

Sample	Dose (µg/disc)	Average Inhibition Zone Diameter (mm) ± STD*	
		E. coli	*S. aerus*
Curcumin	100	6,05 ± 00,8[a]	5,30 ± 0,08[a]
	50	4,60 ± 00,5[b]	3,97 ± 0,08[b]
	25	2,99 ± 0,11[c]	2,49 ± 0,03[c]
	12,5	1,64 ± 0,07[d]	1,04 ± 0,03[d]
Zn(II)-curcumin	100	5,39 ± 0,03[a]	6,09 ± 0,04[a]
	50	3,88 ± 0,03[b]	5,27 ± 0,13[b]
	25	2,59 ± 0,13[c]	3,34 ± 0,06[c]
	12,5	0,97 ± 0,01[d]	1,68 ± 0,12[d]
Control (+) Tetracycline	20	19,88 ± 0,11	14,79 ± 0,16
Control (-) Ethanol		–	–

Remarks: * = average result ± STD
– = no antibacterial activity
Different letters (a, b, c, d) show statistically noticeable differences at $p<0.05$

The data collected from the bacterial test were statistically analyzed by using the Anova test. The results showed a value of $p<0.05$, meaning that the average treatment for the curcumin group is significantly difference from the Zn(II)-curcumin complex group. Therefore, a post-hoc analysis was carried out to find out which groups have these meaningful differences. The results of the post-hoc analysis demonstrated a significant difference between the inhibitory zones formed in *E.coli* and *S.aureus* bacteria, but did not show a significant difference in the inhibitory zones, between curcumin and the Zn(II)-curcumin complex.

Antibacterial activities of both curcumin and the Zn(II)-curcumin complex as well as the positive control are greater against *E.coli* bacteria than *S.aureus*; this is due to differences in the composition and structure of bacterial cell walls that affect their sensitivity. Gram-negative bacteria have a peptidoglycan cell wall of only about 10%, so the cell wall is thinner, in addition to the nature of gram-negative bacteria containing a lot of lipids and porin protein which acts as an entry channel for active substances into bacterial cells. Active substances that enter bacterial cells will damage enzyme activity and cause cell damage, in addition to high lipid levels will increase the permeability of active substances into cells. In the case of the gram-

positive bacteria, their cell walls consist of 70% of peptidoglycans, contain little amount of lipids and the cell walls contain polysaccharides (teichoic acid), causing gram-positive bacteria to be more polar [24]. Teichoic acid is a water-soluble polymer, this water-soluble property indicates that the cell wall of gram-positive bacteria is more polar. Based on the results of the KLT, it shows that the Zn(II)-curcumin complex is slightly more polar than curcumin, so it is suspected that the Zn(II)-curcumin complex is easier to penetrate the polar peptidoglycan layer than the non-polar lipid layer [25].

Zinc metal shows antibacterial activity, because the metal can interact with the bacterial nucleus and its surface where zinc can enter bacterial cells [18]. Meanwhile, the mechanism of curcumin in inhibiting bacterial activity is the same as other phenol compounds, namely by denaturing and damaging cell membranes so that the cell metabolic process is disrupted, then the growth process in bacteria is inhibited, which results in the death of bacteria [26]. The ability of metal-curcumin complexes as antibacterial is better when compared to only metal or curcumin alone, this is due to the increasing content of active compounds that have an antibacterial role so that the antibacterial activity will be greater [27]. The zinc(II)-curcumin complex exhibits the ability to inhibit and kill bacteria through inhibition of cell division, biofilm formation and induce oxidative stress [28].

CONCLUSION

The interaction between curcumin ligands and zinc(II) ions resulted in a compound with characteristic properties presented by UV-Vis and FTIR spectra, different from curcumin alone indicating possible coordination of zinc(II) ion with curcumin in the β-1,3-diketon system. Curcumin and Zn(II)-curcumin complex demonstrate antibacterial activity by forming inhibitory zones in *E.coli* and *S.aureus* bacteria. The best antibacterial activity of curcumin and Zn(II)-curcumin complex against bacteria is at a dose of 100 µg/disc, with the inhibition zone towards *E.coli* bacteria is 6.06 and 5.39 mm, respectively, while the inhibition zone towards *S.aureus* bacteria is 5.30 and 6.09 mm, respectively.

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