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Synthesis, characterization and antibacterial activity of a curcumin–silver(I) complex

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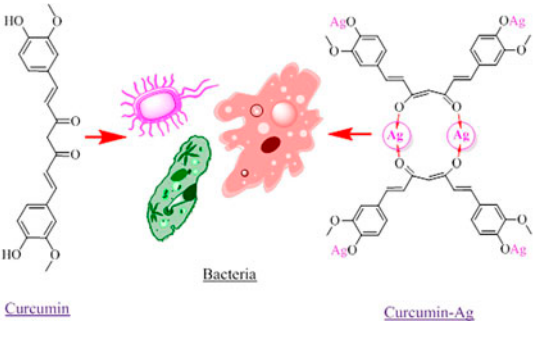

The current study reports the synthesis of a curcumin–silver(I) complex and its preliminary tests against four bacterial strains viz. *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, and *Bacillus cereus* using agar well diffusion method. The results were compared with curcumin by testing it in parallel with the sample. Curcumin showed zones of inhibition against all tested strains of bacteria. Among all bacterial strains, *S. aureus* was the most sensitive to curcumin with zone of inhibition of 12.2 mm. However, the curcumin–Ag(I) complex did not show the expected enhanced activity against all bacteria. This is perhaps due to the replacement of curcumin phenolic protons by silver ions which might have suppressed the antibacterial property of curcumin. The current research findings suggest that while synthesizing curcumin–metal complexes, the phenolic heads may either be left unaltered or need to be replaced by better substituents than hydroxy groups. Based on the current findings, biologically enhanced models have been provided as future recommendations.

Keywords: Curcumin; Curcumin-silver(I) complex; Antibacterial activity

Introduction

Curcumin is a well-known phytochemical due to its biological significance. Several curcumin-based medicines are available in the market for treatment of various diseases. Due to such broad medicinal potential, researchers modify the chemical structure of

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curcumin to further enhance its biological efficacy. Curcumin is a yellow-orange pigment which is extracted from the spice turmeric (botanical name: *Curcuma longa L*). It is commonly called Haldi and is widely used in Unani and Ayurvedic system of medicines [1]. Commercially available curcumin is a mixture of naturally occurring curcuminoids with curcumin (C, ~77%), demethoxycurcumin (DMC, ~18%), and bisdemethoxycurcumin (BDMC, ~5%) [2, 3], see figure S1 (see online supplemental material at http://dx.doi.org/10.1080/00958972.2014.1003051). It has attracted considerable attention due to its wide spectrum of biological and pharmacological activities, including wound healing [4, 5], antioxidant [6, 7], antitumor [8, 9], anti-inflammatory [10, 11], and antibacterial activities [12, 13].

Pure curcumin suppresses the growth of bacteria like *Streptococcus*, *Staphylococcus*, *Lactobacillus*, and many more [14] including human pathogenic fungi. Furthermore, it has been found that the antimicrobial potential of curcumin is large because of its phenolic groups attached at the terminal position [15]. The mechanism of action of phenolic compounds involves interaction of their hydroxyl groups with the cell membrane resulting in cell leakage, alteration of fatty acids and phospholipid profiles, and damage of the energy metabolism and synthesis of genetic materials [16].

The replacement of these phenolic protons by comparatively better substituents may further enhance the biological efficacy of curcumin. For example, Singh and co-workers reported the synthesis of a number of curcumin derivatives by substituting the phenolic protons either with acyl groups containing long alkyl chains or substituents containing several nitrogens (figure 1). The selected compounds showed enhanced antimicrobial and antiviral activity when compared to curcumin. This is perhaps due to increased lipophilicity of the synthesized compounds when compared to curcumin, which could lead potent compounds to cross the microbial cell membrane to let them interact with DNA [17]. However, if the substituents are not suitable when compared to the phenolic group, the biological efficacy may either reduce or completely vanish.

Recently, some metal complexes of curcumin have been synthesized and tested for their biological significance [18, 19]; for example, ruthenium(II) complex **3** [19] and cobalt(II), nickel(II), copper(II), and zinc(II) complexes **4–7** of curcumin [18] (figure 2). It can be noticed that while synthesizing metal complexes **4–7**, the phenolic and methoxy groups of curcumin were not altered. It has been reported that the compounds containing phenolic groups have significant antimicrobial activity [20, 21]. Hence, it might be because of the fact that the phenolic heads have played their part against bacteria [20, 21] in **3–7** (that is significant) and metal centers might have then played a partial role to further enhance their biological potential. Table 1 clearly shows that the MIC values of curcumin are partially enhanced after incorporation of metal [18].

In the current study, we have replaced the phenolic protons of curcumin with sodium and then finally by silver ions as well as coordination of carbonyl groups to silver (scheme 1). Silver has been known as an antimicrobial agent for centuries [22]. It has been used for transport and conservation of drinking water, prevention of burnt skin infections, [23] and treatment of eye infections in new born babies. Silver is a potential antimicrobial agent which is also evident from recent reports [22, 24–28]. The antimicrobial potential of Ag(I) is due to its interaction with nucleic acids and bases in DNA [29, 30]. It was proposed that silver substitution at the phenolic heads may be better than hydroxy groups. The synthesized complex (C, scheme 1) and curcumin were then tested, in parallel, against different pathogenic bacteria.

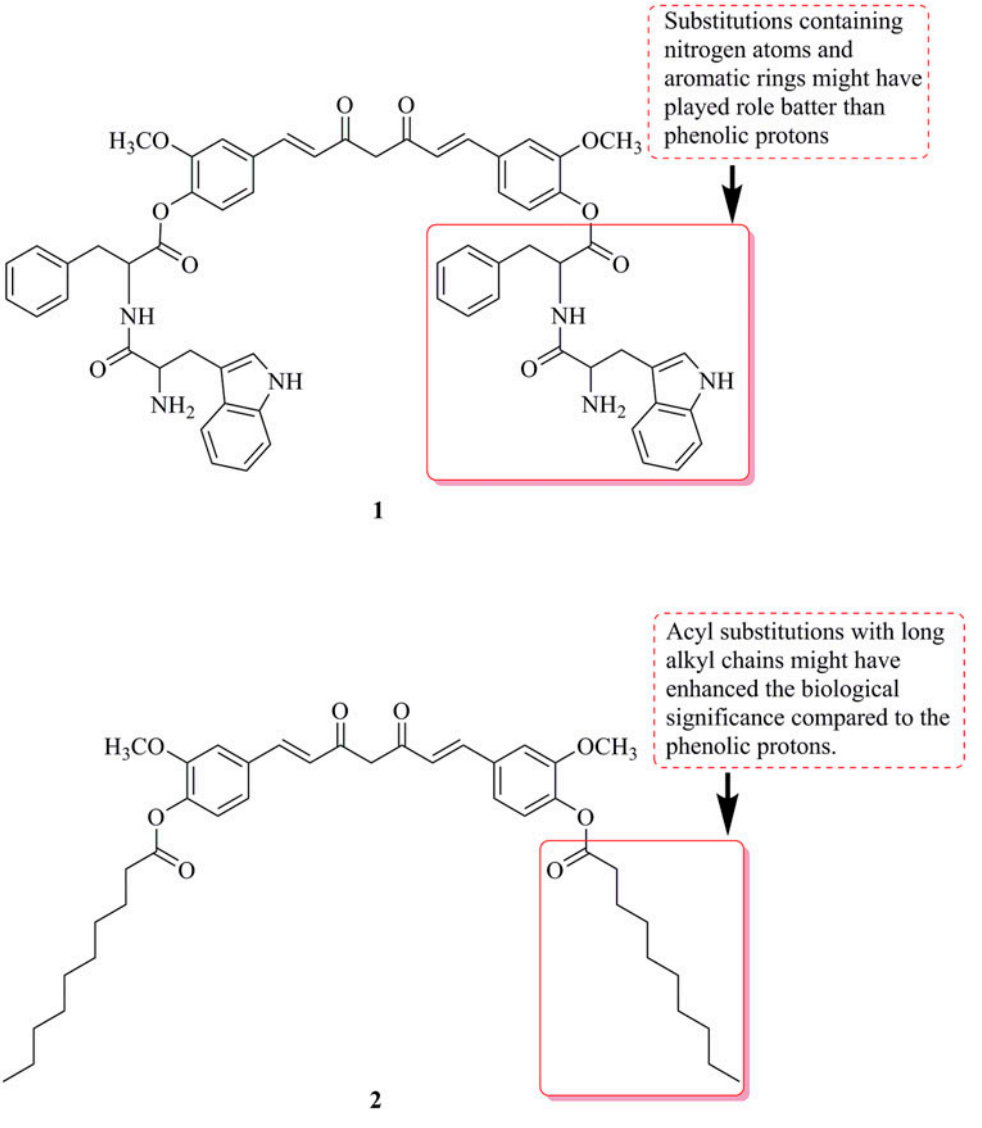


Figure 1. Derivatives of curcumin that have shown enhanced antimicrobial and antiviral activity when compared to curcumin.

Materials and methods

Curcumin (≥95% curcuminoids) was purchased from Natural Remedies Pvt Limited, Bangalore, India. Nutrient agar and nutrient broth medium were purchased from Merck, Germany. Sodium hydride (60%) was purchased from Acros Organics, New Jersey, USA. THF was purchased from Fischer Scientific, UK limited, Leicestershire, UK. Methanol, *n*-hexane, DMSO, and diethyl ether were purchased from Qrec (Asia) SDN BHD, Selangor, Malaysia. Silver nitrate was purchased from R & M Chemicals, Selangor, Malaysia. All

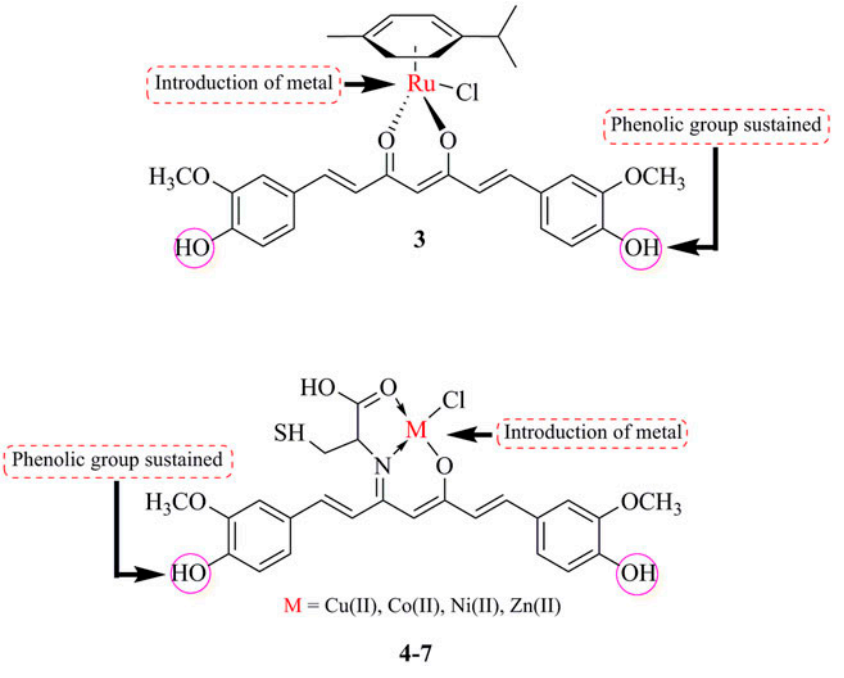


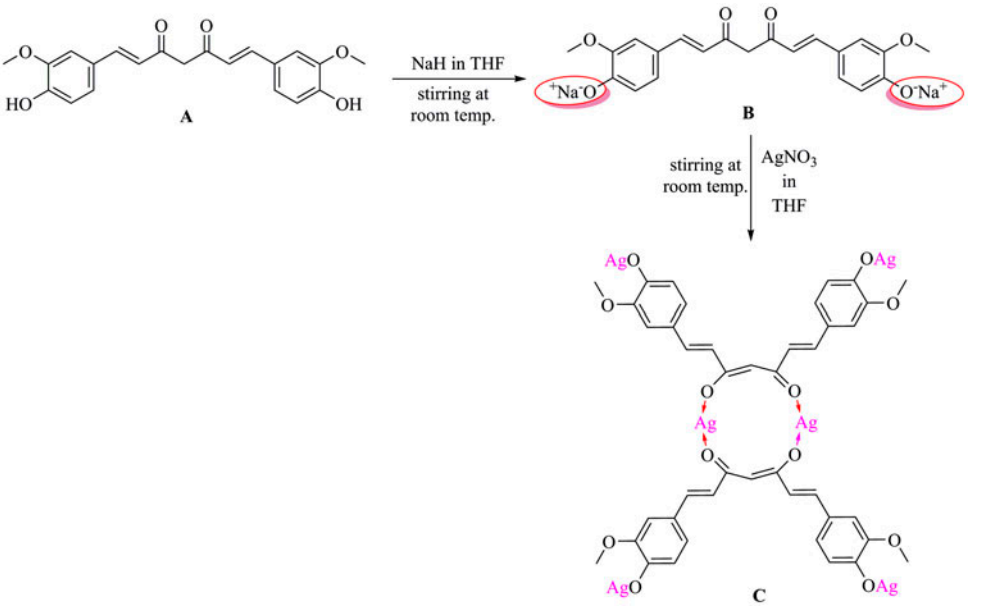
Figure 2. Metal complexes of curcumin that have shown biological significance.

Table 1. Minimum inhibitory concentration (MIC) values of **1**, **2**, and **4**–**12** tested against bacteria.

Compounds	*S. viridans*	*E. coli*	*K. pneumoniae*	*P. mirabilis*		Ref.
Curcumin	2.47	1.23	1.23	1.23		[17]
1	0.43	0.43	0.43	0.43		//
2	0.67	0.33	0.67	0.67		//
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*S. typhi*	
Curcumin	18.1	18.9	17.3	18.6	19.5	[18]
4	12.3	14.1	11.2	11.8	13.9	//
5	12.1	14.3	11.8	12.6	13.4	//
6	12.9	14.8	12.1	12.6	13.8	//
7	13.0	15.0	12.9	12.9	14.2	//
	E. coli	*S. aureus*	*P. aeruginosa*			
8	0.006	N.T.	N.T.			[39]
9	0.006	N.T.	N.T.			//
10	0.005	N.T.	N.T.			//
11	10.2	10.2	10.2			[40]
12	<4.5	8.8	8.8			//

All values are given in micromole (μM) units.
N.T. = not tested.

solvents were of analytical grade. FT-IR and NMR spectra were collected using Perkin Elmer-2000 and Bruker Avance 500 MHz NMR instruments, respectively. Elemental analyses (CHNS/O) were carried out using a Perkin Elmer series II, 2400 CHNS/O analyzer and the contents of silver were determined by using atomic absorption spectrophotometer (AAS) Analyst 400.



Scheme 1. Two step synthesis of Ag–curcumin complex. The scheme shows chemical structures of curcumin (**A**), its sodium salt (**B**), and Ag–curcumin complex (**C**).

Synthesis

The synthesis of the curcumin complex was carried out in two steps (scheme 1). In the first step, curcumin was reacted with sodium hydride in dry THF at room temperature to replace the phenolic protons by sodium ions. During the reaction, effervescence due to H_2 was observed that indicated the successful replacement of phenolic hydrogen with sodium ions. The reaction mixture was filtered using Whatman filter paper No. 10 and washed with fresh THF (dry, 3 × 10 mL). The filtrate was evaporated under vacuum using a rotary evaporator to collect a dark red solid. The obtained solid was recrystallized from methanol/diethyl ether solvent system; a saturated solution of the salt in methanol was exposed to diethyl ether vapors in a closed container. The Na–curcumin salt was collected as a red crystalline material. In the second step, silver nitrate was reacted with purified Na–curcumin salt in dried THF at room temperature. A dark green solution was formed within few minutes. The reaction was allowed to stir at room temperature for 24 h. The reaction mixture was filtered through a pad of Celite and was evaporated under vacuum. The obtained thick viscous material was dried in an oven at 60 °C. The compound was collected as a shiny black crystalline material that was further recrystallized by methanol/*n*-hexane solvent system and was preserved as a shiny black crystalline powder. The Na–curcumin salt was soluble in water at an enhanced amount when compared to curcumin. However, the Ag–curcumin complex was completely insoluble in water but remained soluble in organic solvents like methanol, DMSO, THF, and produced greenish tint in solution form. The crystalline black Ag–curcumin powder is shown in figure S2 (Supplementary material).

Curcumin

Powder, melting point, 155.8 °C, FT-IR (KBr, ν cm^{-1}); 3510 (OH), 3011 (C_{sp2}–H aromatic stretch), 2973, 2942, 2847 (C_{sp3}–H stretch), 1626 (C=O stretch), 1602, 1514, 1457, 1430 (C=C stretch), 1381 (CH_3 bending), 1281, 1232, 1209, 1186 (acyl & phenol C–O bending), 1156, 1026 (alkoxy C–O bending), 965, 856, 814 (alkene C_{sp2}–H bending). ^{13}C NMR (125 MHz, DMSO-d_6); 55.6, 100.8, 111.3, 115.8, 121.0, 123.0, 126.3, 130.3, 140.6, 147.9, 149.3, 159.7, 183.1 (C=O). M.W. = 368.

Na–curcumin

Curcumin (7.37 g, 0.02 M) reacted with sodium hydride (6 eq., 2.88 g, 0.12 M) in dry THF (50 mL) at room temperature (25 ± 2 °C). The reaction mixture was stirred for 6 h, filtered, washed with fresh THF (dry, 3 × 10 mL) and recrystallized from methanol/diethyl ether solvent system. Red crystalline material. Yield, 5.78 g (70%). Melting point, 160.7 °C. FT-IR (KBr, ν cm^{-1}); 3015 (C_{sp2}–H aromatic stretch), 2922, 2855 (C_{sp3}–H stretch), 1628 (C=O stretch), 1603, 1514, 1453, 1426 (C=C stretch), 1378 (CH_3 bending), 1285, 1236, 1209, 1186 (acyl & phenol C-O bending), 1156, 1026 (alkoxy C–O bending), 961, 855, 814 (alkene C_{sp2}–H bending). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6); 55.7, 100.7, 111.1, 115.7, 121.1, 123.2, 126.1, 130.7, 140.5, 147.8, 149.2, 159.6, 183.5 (C=O). M.W. = 412. Anal. Calcd for $C_{21}H_{18}Na_2O_6$ (%): C, 61.8; H, 4.4; O, 23.3. Found (%): C, 61.9; H, 4.6; O, 23.1.

Ag(I)–curcumin

Silver nitrate (10 g, 0.06 M) reacted with the purified Na–curcumin salt (4.12 g, 0.01 M) in dried THF (50 mL) at room temperature (25 ± 2 °C). The reaction mixture was stirred for 24 h. The resulting material was filtered through a pad of Celite (545), evaporated under vacuum, and recrystallized from methanol/*n*-hexane solvent system. Black crystalline material. Yield, 8.37 g (61%). Melting point, 142.3 °C. FT-IR (KBr, ν cm^{-1}); 3011 (C_{sp2}–H aromatic stretch), 2954, 2924, 2853 (C_{sp3}–H stretch), 1590 (C=O–Ag), 1513, 1464, 1450, 1429 (C=C stretch), 1377 (CH_3 bending), 1270, 1205, (acyl and phenol C–O bending), 1163, 1124, 1030 (alkoxy C–O bending), 816, 765 (alkene C_{sp2}–H bending). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6); 48.5, 55.5, 115.6, 125.2, 126.3, 128.1, 128.6, 128.8, 130.2, 137.3, 140.6, 147.9, 149.2, 152.9, 190.4 (C=O–Ag^{109}), 191.0(C=O–Ag^{107}). M.W. = 1379. Anal. Calcd for $C_{42}H_{38}Ag_6O_{12}$ (%): C, 36.5; H, 2.8; O, 13.9; Ag, 46.8. Found (%): C, 36.9; H, 2.9; O, 13.7; Ag, 42.5.

Test microorganisms

Bacterial strains used in the study were clinical isolates of *Staphylococcus aureus*, *Escherechia coli*, *Bacillus subtilis*, and *Bacillus cereus*; all of them were collected from the Pathology, Laboratory, General Hospital, Penang, Malaysia. The bacterial strains were cultivated in nutrient agar slants and preserved at 4 °C.

Preparation of test and standard solutions

Test solutions of the curcumin and Ag–curcumin were prepared in DMSO at 1, 10, and 20 mg/mL. Cefaclor standard was prepared by dissolving of 500 mg of cefaclor in 500 mL DMSO to give a final concentration of 1 mg/mL. DMSO was used as solvent control.

Evaluation of antibacterial activity

The antibacterial activity evaluation was performed by the agar plate diffusion method [31]. Suspensions of all organisms were prepared by using serial dilution method. A 24-h old culture was used for preparation of bacterial suspension. Suspensions of organisms were made in sterile isotonic solution of sodium chloride (0.9% w/v). Nutrient broth and nutrient agar medium were used for the bacterial count and agar well diffusion method, respectively. The sterilized nutrient agar medium was cooled to 40 °C and 20 mL was poured into each petri-plate to obtain 4–6 mm thickness. The test organisms were seeded into respective medium by gently mixing 0.02 mL of the 24-h fresh cultures in sterile petri-plates. The media were allowed to solidify at room temperature. After solidifying, a sterile borer was used to prepare wells of 6 mm diameter in the agar media spread with the micro-organisms. The wells were filled with 0.06 mL of the three tested concentrations (1, 10, and 20 mg/mL). Plates were allowed to stand at room temperature to let the samples diffuse into the agar and afterwards, the plates were incubated at 37 °C for 24 h. The diameter of the zone of inhibition around each well was taken as a measure of the antibacterial activity. Each experiment was carried out in duplicate and mean diameter of the inhibition zone was recorded in millimeters. The solvent control was run simultaneously to assess the activity of DMSO, which was used as a solvent for curcumin and Ag–curcumin.

Results and discussion

Chemistry

The synthesis of required Ag–curcumin complex was carried out in two steps. The intermediate as well as final products were characterized by FT-IR and NMR spectroscopies. The contents of silver in curcumin–Ag(I) complex were determined using AAS whereas the % contents of carbon, hydrogen, and oxygen were determined by CHNS/O analyzer.

FT-IR spectroscopy

The starting material (curcumin) and synthesized compounds (Na–curcumin and Ag–curcumin) were characterized by FT-IR to observe the possible changes in the spectral features. The spectral differences of curcumin and Ag–curcumin are shown in figure 3. The spectrum A (of curcumin) showed a sharp vibrational band “a” possibly due to phenolic OH [32]. This vibration was absent in Na–curcumin and Ag–curcumin (spectrum B) due to the replacement of phenolic proton by Na and Ag ions, respectively. This phenomenon can also be observed by noticing slightly different vibrational bands (in spectrum A and B) at 1100–1300 cm^{-1} (marked as “b”

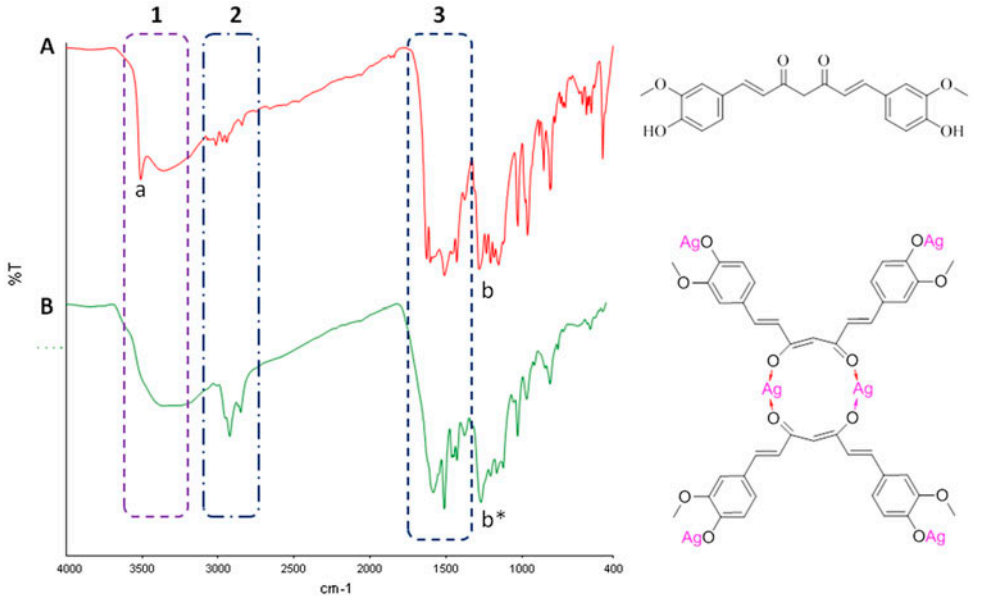


Figure 3. FT-IR spectral features of curcumin (spectrum A) and Ag–curcumin (spectrum B) in comparison. The spectra indicated significant changes in support of proposed complex. For example, the disappearance of phenolic vibration "a" in spectrum B and vibrational changes in the highlighted region **3** indicated the bonding of oxygen to silver ions.

and "b*") which appeared due to alkoxy as well as phenol C–O bending [32]. The enhanced vibrational bands at 1270 cm^{-1} (b*) indicated the attachment of silver at the (terminal) phenolic oxygen of curcumin. Also, several spectral changes from 500 to 900 cm^{-1} can also be seen. Importantly, the most significant spectral changes were observed in the selected region **3** (1400–1650 cm^{-1}). In these spectra, this region is specific for carbonyl as well as C=C ring stretch. Significant changes can be seen in the spectrum B when compared to A in region **3**. Spectrum B clearly shows that C=O peak has moved to lower frequency (1590 cm^{-1}) and is broader than this peak in curcumin (Spectrum A, 1626 cm^{-1}). This indicated coordination of carbonyl group with silver ions [33–37], as shown in scheme 1.

FT-NMR spectroscopy

To further characterize the complex, ^{13}C NMR spectra of curcumin and Ag–curcumin were collected. Whenever carbonyl coordinates to any metal ion, its carbonyl carbon signal moves downfield when compared to the free carbonyl carbon chemical shift [33]. In the ^{13}C NMR spectrum of curcumin, the carbonyl peak was at $\delta = 183.1$ ppm. However, in Ag–curcumin complex this peak moved ~7 ppm downfield as two chemical shifts, $\delta = 190.4$ and 191.0 ppm, appeared (figure 4). The appearance of two signals might be due to isotopic (^{107}Ag and ^{109}Ag) coordination of silver with carbonyl [38–40]. Nevertheless, the movement of carbonyl chemical shifts to relatively downfield region (*ca.* 190 ppm) indicated coordination of carbonyl to silver ions.

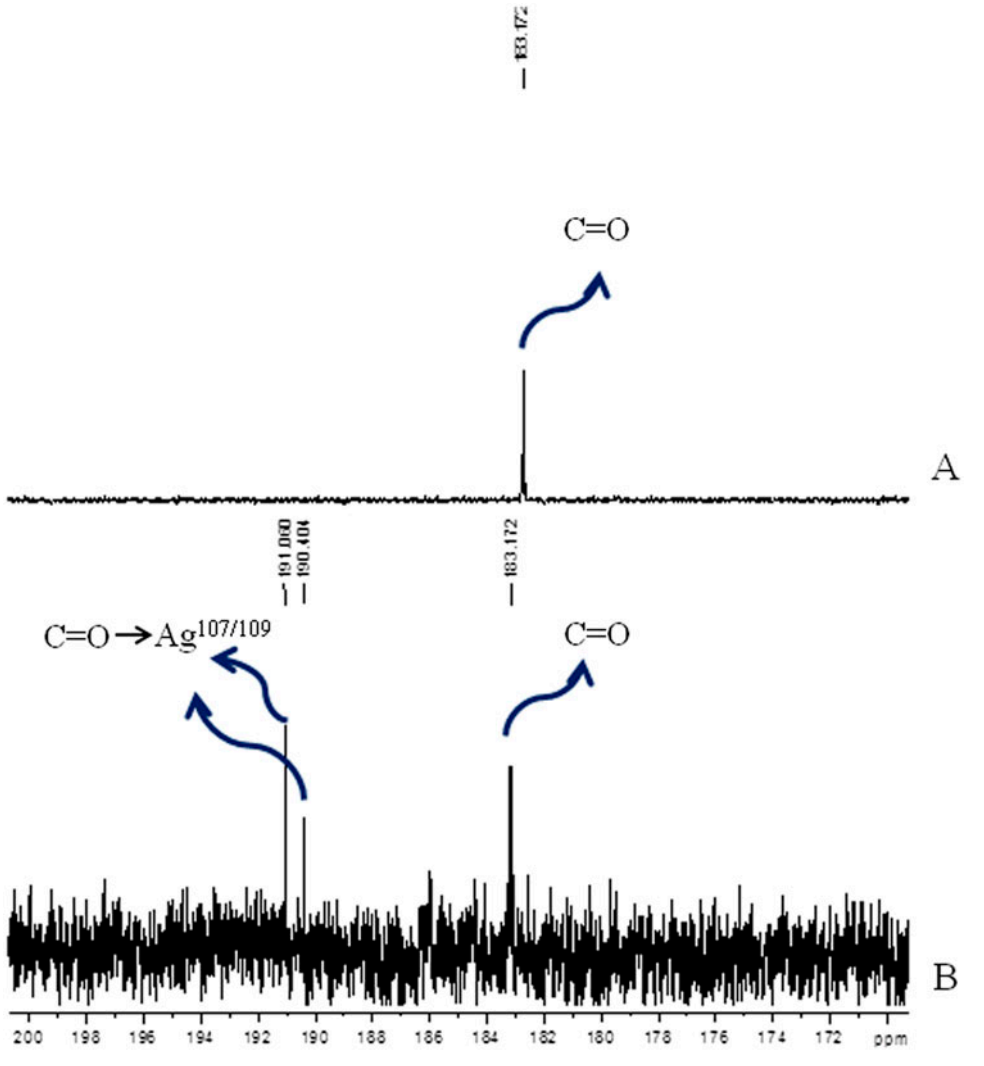


Figure 4. The ^{13}C NMR selected regions (δ = 170–200 ppm) of pure curcumin (A) and Ag–curcumin complex (B). The spectrum B was collected from the reaction mixture after 1 h of stirring at room temperature to know the reaction progress. The appearance of two new peaks, at *ca.* 190 ppm, indicated the coordination of carbonyl group with silver ions.

Biological studies

Some silver complexes **8–12** (chart 1) of ligands other than curcumin were reported to have significant antimicrobial activity [41, 42]. For example, **8–10** were synthesized and tested against *E. coli*. The complexes were found to have potent antimicrobial activity (MIC = 0.01 mM). However, the IC_{50} value of **10** was better (0.005 μM) when compared with **8** and **9** (IC_{50} = 0.006 μM) [41]. Similarly, silver complexes **10–12** were reported by Velluti and co-workers [42] and were tested against three types of bacteria (*S. aureus*, *E. coli*, and *P. aeruginosa*). Both complexes showed significant antimicrobial inhibition

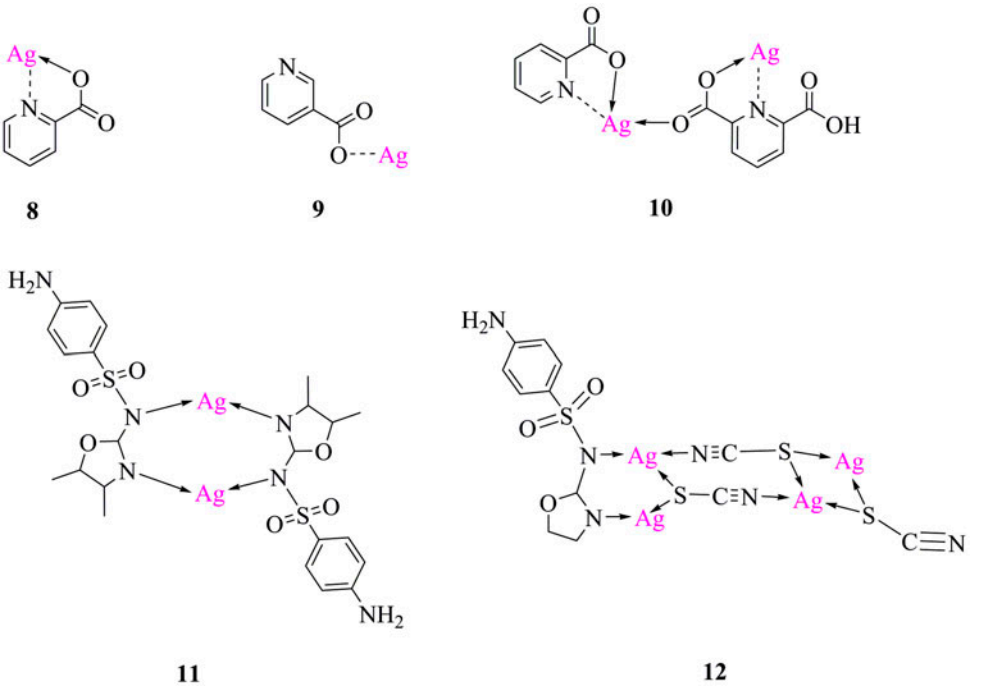


Chart 1. Silver complexes from the literature which have been tested against various bacteria. **8** ($AgC_6H_4NO_2$), **9** ($AgC_6H_4NO_2$), **10** ($AgC_7H_{5.5}O_{4.75}N$), **11** ($Ag_2C_{22}H_{26}N_6O_4S_2$), **12** ($Ag_4C_{14}H_{14}N_6O_4S_4$).

Table 2. Zone of inhibition (in mm).

Test compounds	Conc. (mg/mL)	*S. aureus*	*E. coli*	*B. subtilis*	*B. cereus*
Curcumin	20	12.2	9	9.5	9
	10	12	8	9.1	8
	1	10	8	8	7
Ag–curcumin	20	0	0	0	0
	10	0	0	0	0
	1	0	0	0	0

whereas **12** remained comparatively active (MIC = 8.8 μM against *S. aureus*, <4.5 μM against *E. coli*, and 8.8 μM against *P. aeruginosa*) when compared to **11** (MIC = 10.2 μM against *S. aureus*, 10.2 μM against *E. coli*, and 10.2 μM against *P. aeruginosa*).

The antimicrobial test results of curcumin and Ag–curcumin by using the well diffusion method [31] are shown in figure S3. The efficiency of the drug was measured by the zone of inhibition (in mm) of the bacteria cultured on the agar plate. Curcumin exhibited an inhibition zone (black color arrows) whereas Ag–curcumin did not (yellow colored arrows). The results are summarized in table 2. Ag–curcumin was inactive (zone of inhibition = 0 mm) for all bacteria in different concentrations. However, curcumin showed activity against all types. At higher concentrations, curcumin has more activity against *S. aureus* with zone of inhibition of 12.2 and 12 mm. Curcumin showed approximately similar activity against *E. coli*, *B. subtilis*, and *B. cereus* at all concentrations as shown in table 2.

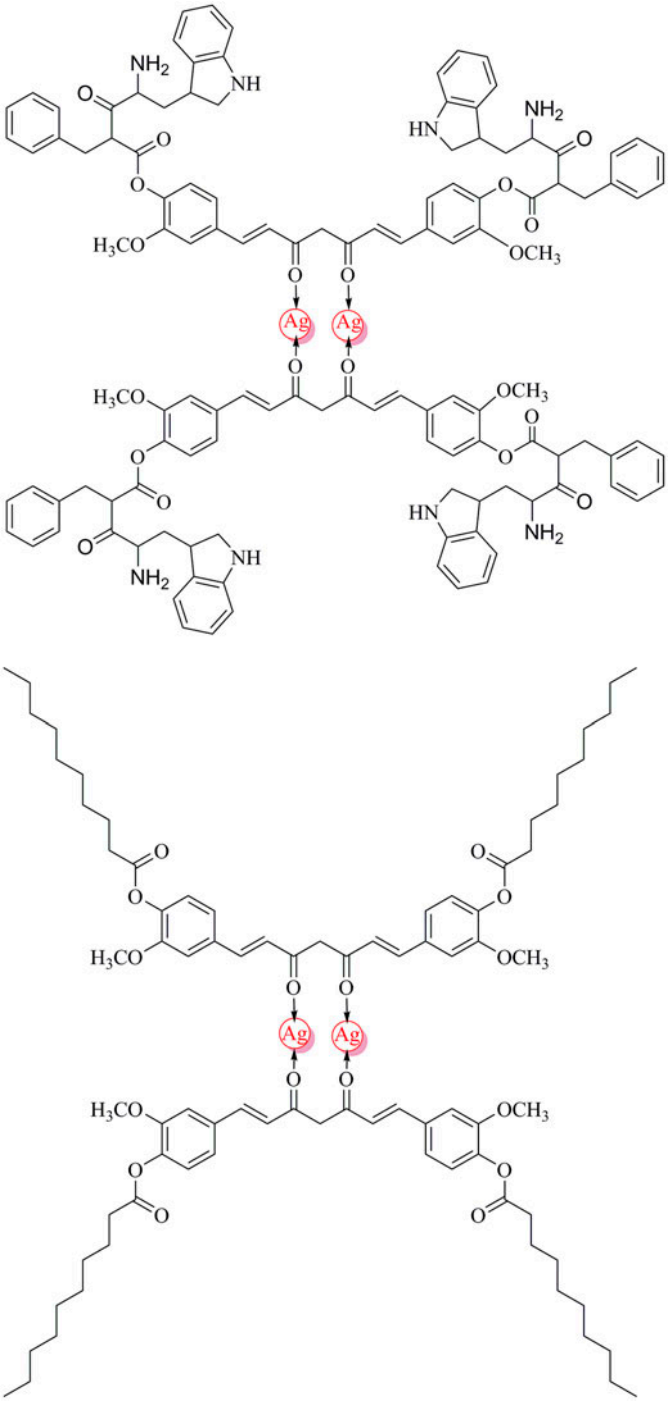


Figure 5. The proposed Ag–curcumin complexes that may have biological significance better than curcumin.

Pure curcumin is a potential antimicrobial agent mainly due to its terminal phenolic groups [15]. So the replacement of these phenolic protons, the most convenient substitution site, will be fruitful only if the substitution plays a better role than phenol in curcumin as described in the introduction. However, if the substitutions are not suitable when compared to the phenolic heads, the activity may either reduce or completely vanish (figure 5).

In recent reports of metal complexes of curcumin (figure 2), the phenolic heads were not altered and the complexes showed improved results when compared to curcumin [18, 19]. In the current study, we have replaced the phenolic protons by silver ions (scheme 1) with the intention that silver may play a significant role when compared with the phenolic heads. However, the results showed that this substitution is not productive. It further provides clear indication that while synthesizing curcumin metal complexes, the phenolic heads may be altered or not and can then be complexed with a suitable metal ion.

Conclusion

In the light of literature and current research, it can be concluded that while synthesizing curcumin-based metal complexes its active heads (phenolic and methoxy) may not be altered or altered to an enhanced form since the metals play a partial role in further enhancing its efficacy. In the present synthesis, the phenolic heads were replaced by less favorable substitutions, so the complex could not inhibit the growth of bacteria whereas curcumin could inhibit due to the presence of phenolic heads.

Future recommendations

In future, ligands of types **1** and **2** (figure 1) may be more favorable for the synthesis of curcumin-silver(I) complexes since such ligands are already biologically enhanced forms of curcumin. The coordination of silver at carbonyl groups may further participate in the biological significance of these curcumin derivatives. The general design of proposed complexes is given in figure 5.

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