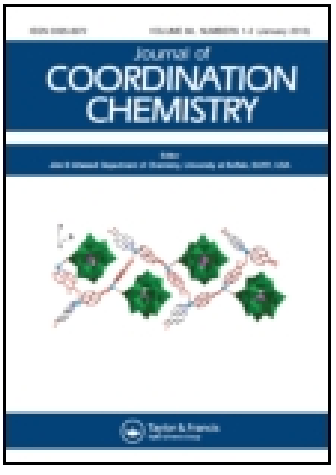

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Valapatukutikadan Davis John [a], Muhammed Basheer Ummathur [b] & Krishnannair Krishnankutty [c]

[a] Department of Chemistry, Christ College, Irinjalakuda, India

[b] Department of Chemistry, KAHM Unity Women's College, Manjeri, India

[c] Department of Chemistry, University of Calicut, Thenhipalam, India

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Synthesis, characterization, and antitumour studies of some curcuminoid analogues and their aluminum complexes

VALAPATUKUTIKADAN DAVIS JOHN†, MUHAMMED BASHEER UMMATHUR*‡ and KRISHNANNAIR KRISHNANKUTTY§

†Department of Chemistry, Christ College, Irinjalakuda, India
‡Department of Chemistry, KAHM Unity Women's College, Manjeri, India
§Department of Chemistry, University of Calicut, Thenhipalam, India

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Aluminum(III) complexes of three curcuminoid analogues [1,7-diphenyl-1,6-heptadiene-3,5-dione, HL^1; 1,7-bis(2-hydroxyphenyl)-1,6-heptadiene-3,5-dione, HL^2; and 1,7-bis(4-ethoxyphenyl)-1,6-heptadiene-3,5-dione, HL^3] of [AlL_3] stoichiometry were synthesized and characterized by UV, IR, ^{1}H NMR, and mass spectral data. The compounds were investigated for cytotoxic and antitumor activities. The aluminum chelates are remarkably active compared to free curcuminoid analogues. The aluminum complex of HL^2 with hydroxyl in the phenyl ring was most active towards Ehrlich ascites carcinoma cells (concentration needed for 50% inhibition of 5 μg/mL) and cultured L929 cells (1 μg/mL produced 60 + 3% cell death). Increase in lifespan and reduction of solid tumor volume in mice were also largest for the aluminum complex of HL^2. The study reveals that the antitumor activities of curcuminoids are more enhanced by complexation with aluminum than with transition metal ions.

Keywords: Curcuminoids; Aluminum complexes; Cytotoxic and antitumor activities; Spectral studies

1. Introduction

Curcuminoids (1,7-diaryl-1,6-heptadiene-3,5-diones), extracted from the rhizomes of the traditional Indian medicinal plant turmeric (*Curcuma longa*, Linn., *Zingiberacea* family), have been reported to possess antiinflammatory, antioxidant, antiarthritic, and antitumor activities [1–4]. Presence of phenolic group together with the conjugated β-diketone structure is responsible for their high biological activity and this led to further studies using structurally related compounds [5–8]. Medicinal importance of many plant chemicals is enhanced by complex formation with various metal ions [9]. Metal complexation of these unsaturated 1,3-diketones led to dramatic changes in their biochemical properties including antitumor activity [10, 11].

Heavy metals, as poisons, were not assumed to act as potential anticancer drugs because of their toxicity. The earliest attempt to introduce metals in the drug development was the

*Corresponding author. Email: mbummathur@gmail.com

so-called Fowler's solution, arsenotherapy [12]. Some similar compounds are still used today, such as As_2O_3 [13]. The effect of a heavy metal on cancer is not only due to the metal alone but also due to the structure and the type of compounds [14]. Historically, metals and metal complexes have played a key role in the development of pharmacy and modern chemotherapy. However, they still remain a tiny minority of all therapeutics on the market today [15]. There are many known and documented heavy metal complexes that carry photochemical, anticancer, or both activities [16].

Interest in aluminum has considerably increased due to its potential toxic effects [17–20]. The effects of aluminum are highly dependent upon the chemical form as well as the concentration in which this element enters the biological system.

Chelation therapy is the preferred medical treatment for reducing the toxic effects of metals [21]. Thus toxic heavy metals can be removed from the body through complexation with curcumin [22]. Recent studies have shown that curcumin has neuroprotective effects against aluminum-induced cognitive dysfunction and oxidative damage in rats [23]. Even though literature is extensive on metal complexes of β-diketones, very few reports exist on aluminum β-diketonates [24, 25].

The antitumor activities of natural and synthetic curcuminoids are enhanced by complexation with some transition metal ions [26–29], even though these metal ions themselves are toxic [30]; but reports are scanty on the antitumor studies of non-transition metal complexes of synthetic curcuminoids [31].

As part of our studies on chemical and biochemical activities of synthetic curcuminoid analogues and their metal complexes [26–29, 31–33], the present study reports the synthesis, structural characterization, and antitumor activities of three new curcuminoid analogues and their Al(III) complexes.

2. Experimental

2.1. *Materials and methods*

Carbon and hydrogen were determined by microanalyses (Heraeus Elemental analyzer) and metal contents by AAS (Perkin Elmer 2380 spectrometer). Electronic spectra of the compounds in methanol (10^{-4} mol/L) were recorded on a 1601 Shimadzu UV–vis. spectrophotometer, IR spectra (KBr disks) on a 8101 Shimadzu FTIR spectrophotometer, ^{1}H NMR spectra ($CDCl_3$ or DMSO-d_6) on a Varian 300 NMR spectrometer, and mass spectra on a Jeol/SX-102 mass spectrometer (FAB using argon and *meta*-nitrobenzyl alcohol as the matrix). Molar conductances of the complexes were determined in DMF ($\sim 10^{-3}$ mol/L) at room temperature.

Eagle's minimum essential medium (MEM) and trypsin were obtained from Himedia Laboratories Private Ltd. (Mumbai). Qualigen's silicagel G and silicagel 60–120 mesh were used for analytical TLC and column chromatography, respectively. Tributyl borate was procured from Fluka. All other reagents were of analytical reagent grade.

Ehrlich ascites carcinoma (EAC) cells were obtained from the Cancer Research Institute, Mumbai, India; Dalton's Lymphoma ascites (DLA) cells from the Cancer Institute, Adyar, India; and L929 cells from National facility for animal cell and tissue culture, Pune, India. EAC and DLA were maintained as ascites tumors in Swiss albino mice. L929 cells were maintained in culture using MEM containing 10% goat serum and antibiotics.

Swiss albino mice were purchased from the Veterinary College, Thrissur, Kerala, India. They were fed with normal mouse chow (Lipton India) and water *ad libitum*.

2.2. *Synthesis of curcuminoids*

The curcuminoid analogues were prepared by condensation of aromatic aldehydes (benzaldehyde, salicylaldehyde and 4-ethoxybenzaldehyde) with acetylacetone-boric oxide complex in ethylacetate in the presence of tri(*sec*-butyl)borate and *n*-butyl amine as reported earlier [28,32,34].

To a stirred mixture of acetylacetone (0.005 mol, 0.5 g) and boric oxide (0.0035 mol, 0.25 g) in dry ethylacetate kept at ~80 °C, the aromatic aldehyde (0.01 mol) was added and stirring was continued for ~1 h with the addition of *n*-butyl amine (0.1 mL dissolved in 1 mL dry ethylacetate) dropwise. Stirring was continued for an additional 4 h and the solution was set aside overnight. Hot (~60 °C) HCl (0.4 mol, 7 mL) was added and the mixture was again stirred for 1 h. Two layers were separated and the organic layer was extracted with ethylacetate. The combined extracts were evaporated and the residual paste was stirred with HCl (50%, 10 mL) for ~1 h. The solid product was collected, washed with water, and dried in vacuum. TLC of the product revealed the presence of two components and was quantitatively separated by column chromatography using silica gel (60–120 mesh) as detailed below.

The solid product obtained was dissolved in a minimum quantity of ethylacetate and placed over a column (2 × 100 cm) densely packed with silica gel. The eluting solvent was 1 : 5 (v/v) acetone:chloroform. As the elution proceeded, two bands developed in the column, a pale yellow lower band and orange red upper band. The eluates from the pale yellow lower region and the junction between the two bands were discarded. The elution was then repeated using a 1 : 2 (v/v) mixture of acetone and chloroform to recover the orange red band retained in the upper portion of the column. The eluates were collected in aliquots of 10 mL in separate tubes, checked by TLC; and the combined extracts on removing the solvent in vacuum yielded 1,7-diarylheptanoids (50–70%). They were recrystallized twice from hot benzene to get chromatographically (TLC) pure material.

2.3. *Synthesis of aluminum complexes*

A methanolic solution of aluminum nitrate $Al(NO_3)_3 \cdot 9H_2O$ (25 mL, 0.01 mol) was added with stirring to a solution of curcuminoid (25 mL, 0.03 mol) in methanol. The mixture was refluxed gently for 1 h. After reducing the volume to half, the solution was cooled to room temperature, the precipitated complex was filtered, washed with 1 : 1 methanol–water mixture, and recrystallized from hot methanol.

2.4. *Antitumor experiments*

2.4.1. Determination of short-term *in vitro* cytotoxicity. EAC cells were used for *in vitro* cytotoxic studies. The compounds were dissolved in minimum DMSO which does not enhance cytotoxicity [35–37]. The tumor cells aspirated from the peritoneal cavity of tumor-bearing mice were washed with PBS (phosphate buffered saline). The cell suspension (1×10^6 cells in 0.1 mL) was added to tubes containing various concentrations (1–50 μg/mL) of the compounds and volume was made up to 1 mL using PBS. The mixture was incubated for 3 h at 37 °C and the percentage of dead cells was evaluated by trypan blue dye exclusion method [29,38].

2.4.2. Determination of cytotoxicity of compounds in tissue culture. L929 cells were used for tissue culture studies. The cells (5×10^3 cells/well) were plated in tarzon's 96 well flat-bottomed titer plates and incubated at 37 °C in 5% CO_2 atmosphere. After 24 h of incubation, various concentrations (1–10 μg/mL) of compounds were added to the wells and incubated for a further 48 h. After incubation, the cells were detached by trypsinization (0.2%) and stained with crystal violet. The cytotoxicity was calculated by measuring the optical density at 570 nm after eluting the dye from the cells [29].

2.4.3. Determination of tumor-reducing activity. Groups of Swiss albino mice (6 per group) were injected intraperitonially (ip) with Ehrlich ascites tumor cells (1×10^6 cells/animal). The animals were injected (ip) with test compounds (200 μmoles/kg body weight) suspended in gum accasia and the injections were continued for 10 days. The mortality rate of the mice was noted in each group and the percentage increase in lifespan (%ILS) of the treated group was calculated using the formula $\%ILS = [100(T-C)]/C$, where T is the mean survival time of the treated mice and C is that of the control expressed in days [29].

2.4.4. Determination of the effect of compounds on solid tumor development. The effect of various compounds on solid tumor development was studied using Swiss albino mice. Groups of mice (6 per group) were injected subcutaneously with DLA cells (10^6 cells in 0.1 mL) on the right hind limbs. One group was kept as control and the other groups were injected (ip) with test compounds (200 μmoles/kg body weight) and the injections were continued for 10 days. Tumor diameter was measured every third day for one month and tumor volume was calculated using the formula $V = 4/3\pi r_1 r_2^2$, where r_1 and r_2 are the minor and major radii, respectively [38, 39].

3. Results and discussion

3.1. *Structural characterization of curcuminoids (HL) and their aluminum complexes*

The elemental analytical data of curcuminoids (table 1) suggest that the condensation between acetylacetone and aromatic aldehydes has occurred in 1 : 2 ratio as in figure 1. They formed stable and well-defined crystalline complexes with Al^{3+}. The analytical data of the complexes together with non-electrolytic nature in DMF (specific conductance $<10\,\Omega^{-1}cm^{-1}$; 10^{-3} M solution) suggest [AlL_3] stoichiometry (table 1). The observed analytical and spectral data of the complexes are in conformity with figure 2.

Table 1. Physical and analytical data of curcuminoids and their Al(III) complexes.

				Elemental analysis: found (calculated) %		
Compound/molecular formula	Color	Yield %	m.p. °C	C	H	Al
HL^1 $C_{19}H_{16}O_2$	Pale yellow	60	118	82.66 (82.61)	5.78 (5.80)	–
HL^2 $C_{19}H_{16}O_4$	Dirty green	50	120	74.31 (74.03)	5.35 (5.19)	–
HL^3 $C_{23}H_{24}O_4$	Reddish yellow	70	138	75.83 (75.82)	6.81 (6.59)	–
$[Al(L^1)_3]$ $C_{57}H_{45}AlO_6$	Deep yellow	70	244	80.12 (80.28)	5.22 (5.28)	3.13 (3.17)
$[Al(L^2)_3]$ $C_{57}H_{45}AlO_{12}$	Dark green	60	272	72.02 (72.15)	4.72 (4.75)	2.84 (2.85)
$[Al(L^3)_3]$ $C_{69}H_{69}AlO_{12}$	Dark red	65	280	74.24 (74.19)	6.14 (6.18)	2.39 (2.42)

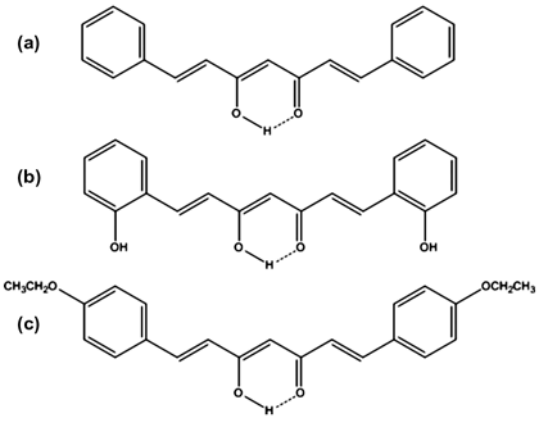

Figure 1. Structure of curcuminoid analogues (HL). (a) 1,7-diphenyl-1,6-heptadiene-3,5-dione (HL^1); (b) 1,7-bis (2-hydroxyphenyl)-1,6-heptadiene-3,5-dione (HL^2); (c) 1,7-bis(4-ethoxyphenyl)-1,6-heptadiene-3,5-dione (HL^3).

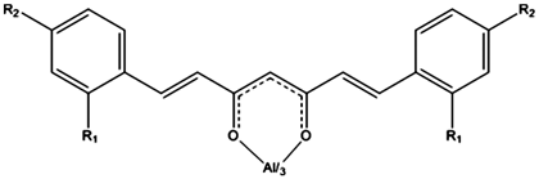

Figure 2. Structure of the alumnium complexes of curcuminoids.

	R_1	R_2
$[Al(L^1)_3]$	H	H
$[Al(L^2)_3]$	OH	H
$[Al(L^3)_3]$	H	OCH_2CH_3

3.1.1. IR spectra. The IR spectra of curcuminoids show a strong band at $\sim$1625 cm^{-1} and a broad band at 2800–3500 cm^{-1} due to the stretching of the chelated carbonyl and the intramolecularly hydrogen-bonded enol, respectively [28, 32, 40]. The absence of any band assignable to a normal α,β-unsaturated carbonyl at 1640–1740 cm^{-1} indicates the existence of the compounds entirely in the enolic form [40] (figure 1). In IR spectra of Al (III) complexes, the band at $\sim$1625 cm^{-1} due to the stretch of carbonyl is absent and, instead, a strong band assignable to the stretch of the coordinated carbonyl is at $\sim$1590 cm^{-1}. The broad band at 2800–3500 cm^{-1} disappeared, indicating the replacement of enolic proton by metal during complexation [41]. However, the spectrum of the complex of HL^2 exhibited bands at 3200–3600 cm^{-1} due to OH stretch in the phenyl ring [28]. This suggests that only the enol proton is replaced by Al^{3+} and the phenolic OH does not coordinate. The prominent band at $\sim$970 cm^{-1} is typical of a *trans* –CH=CH– which remained unaltered in the spectra of metal complexes. That carbonyl groups are involved in bonding with the metal ion is further supported by the appearance of two medium intensity bands at $\sim$420 and $\sim$470 cm^{-1} assignable to $\nu_{Al\text{-}O}$ [28, 41].

3.1.2. ^{1}H NMR spectra. The ^{1}H NMR spectra of curcuminoids displayed a characteristic downfield singlet at $\sim\delta$16 ppm due to intramolecularly hydrogen-bonded enolic proton [28,32,42] (figure 1). The methine proton signal is at $\sim\delta$5.8 ppm. In ^{1}H NMR spectra of the Al(III) complexes, the low field signal at δ16 ppm of the ligand is absent, indicating its replacement by the metal ion during complexation [28]. The methine proton shifted appreciably to low field compared to the shift in the olefinic protons due to the aromatic character of the C_3O_2Al ring system of the chelates by the highly conjugated groups attached to the dicarbonyl. The alkenyl proton signals with a J value of $\sim$16 Hz suggest the *trans* alkene double bond, as in the free ligands [28]. Aryl protons are at δ7.2–8.3 ppm as a complex multiplet. The integrated intensities of various signals agree well with figure 2 of the complexes. That the phenolic OH is not involved in complex formation is clearly indicated [28] in the spectrum of the complex of HL^2 where the signal remains unaltered.

3.1.3. Mass spectra. The FAB mass spectra of curcuminoids show intense molecular ion $P^+/(P+1)^+$ peaks. Peaks due to the elimination of O, OH, H_2O, C_3HO_2, and ArCH-CHCO species from the molecular ion are also characteristic of the spectra [28, 32]. In their mass spectra, all the complexes showed relatively intense $(P+1)^+$ peaks corresponding to $[AlL_3]$ stoichiometry. Peaks due to $[AlL]^+$, $[AlL_2]^+$, L^+, and fragments of L^+ are sometimes more intense. Peaks at m/z corresponding to $[P-n\text{Ar}]^+$, where $n=1$ to 6, are also present in the spectra of metal chelates due to stepwise elimination of aryl groups [10].

3.1.4. UV spectra. UV spectra of curcuminoids exhibit two absorption maxima at $\sim$380 and $\sim$260 nm assignable to various $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ transitions of the highly conjugated molecule [28, 32]. The absorption maxima of the metal chelates bear close resemblance with free ligands, indicating that no structural alteration of the ligand has occurred during complexation. However, the values shifted slightly to longer wavelength ($\sim$10 nm), indicat-

Table 2. Spectral data of curcuminoids and their Al(III) complexes.

Compound	IR stretching bands (cm^{-1})			^{1}H NMR spectral data (δ, ppm)				Mass spectral data, m/z
	C=O	CH=CH *trans*	M–O	Enolic OH	Methine	Alkenyl	Aryl	
HL^1	1612	972	–	16.86	5.9	6.5–7.5	7.6–8.2	276, 199, 173, 145, 131, 103, 102
HL^2	1630	978	–	15.86 10.44*	5.9	6.5–7.5	7.4–8.1	308, 291, 273, 187, 147, 120, 108
HL^3	1628	970	–	16.08	5.8	6.5–7.6	6.9–7.5	365, 346, 217, 189, 175, 147, 146, 134, 121
$[Al(L^1)_3]$	1580	975	461 425	–	6.3	6.6–7.8	7.2–8.0	853, 775, 698, 621, 544, 467, 390, 721, 590, 459, 276, 199, 173, 145
$[Al(L^2)_3]$	1593	970	469 427	– 10.43*	6.4	6.7–7.2	7.5–7.9	949, 855, 762, 669, 576, 483, 390, 807, 654, 360, 308, 215, 189, 161
$[Al(L^3)_3]$	1595	972	468 419	–	6.4	6.6–7.6	7.4–8.3	1117, 995, 874, 753, 632, 511, 390, 941, 820, 578, 364, 243, 122

*Phenolic proton.

ing the involvement of the carbonyl group in metal complexation [10]. Spectral details are given in table 2.

3.2. *Antitumor studies*

3.2.1. Short-term *in vitro* cytotoxicity. The results of short-term *in vitro* cytotoxicity of curcuminoids and their aluminum(III) complexes towards Ehrlich ascites cells shown in table 3 indicate that metal chelation enhances cytotoxicity considerably. Among the compounds subjected to short-term assay, the aluminum complex of HL^2, with a hydroxyl group in the phenyl ring, is most active and HL^1, which possesses unsubstituted benzene ring system, shows low activity (figure 3 and Supplementary material).

3.2.2. Cytotoxicity of compounds in tissue culture. The results of the cytotoxicity of curcuminoids and their aluminum complexes towards cultured L929 cells given in table 4 also indicate that the aluminum chelates are more cytotoxic than the respective curcuminoids. Compound HL^1 is the least active and aluminum complex of HL^2 is the most active (Supplementary material).

Table 3. Short-term *in vitro* cytotoxicity of compounds towards Ehrlich ascites cells.

	% cell death at different concentrations				
Compounds	1 μg/ml	5 μg/ml	10 μg/ml	25 μg/ml	50 μg/ml
HL^1	14	30	35	55	71
HL^2	26	46	64	78	94
HL^3	23	44	50	70	85
$[Al(L^1)_3]$	21	44	57	65	82
$[Al(L^2)_3]$	34	57	79	100	100
$[Al(L^3)_3]$	31	53	77	100	100

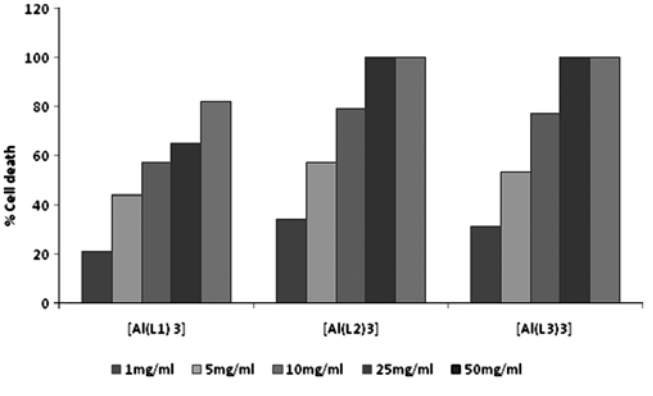

Figure 3. *In vitro* cytotoxic activity of aluminum complexes of curcuminoids towards Ehrlich ascites cells.

Table 4. Cytotoxicity of compounds towards tissue-cultured L929 cells.

Compounds	% cell death at different concentrations			
	1 μg/mL	2.5 μg/mL	5 μg/mL	10 μg/mL
HL^1	15.9 ± 1.5	20.2 ± 1.3	28.1 ± 2.0	39.4 ± 1.3
HL^2	32.9 ± 1.0	37.7 ± 2.8	43.9 ± 2.2	55.6 ± 2.7
HL^3	29.2 ± 2.8	31.3 ± 1.6	37.1 ± 1.9	50.6 ± 2.9
$[Al(L^1)_3]$	28.7 ± 1.3	33.1 ± 1.8	45.8 ± 1.7	53.4 ± 1.9
$[Al(L^2)_3]$	60.1 ± 2.9	63.9 ± 2.4	72.6 ± 2.9	91.2 ± 3.1
$[Al(L^3)_3]$	47.2 ± 1.8	52.3 ± 1.7	58.4 ± 2.4	66.7 ± 1.6

3.2.3. Effect of compounds on ascites tumor reduction. All the compounds when administered ip produced significant increase ($p < 0.001$ from normal) in the lifespan of mice bearing ascites tumors (table 5). Aluminum(III) complexes produced a considerable increase in lifespan of tumor-bearing mice compared with curcuminoids. The percentage increase in lifespan (%ILS) of tumor-bearing mice was found minimum for HL^1 and maximum for aluminum complex of HL^2 (figure 4 and Supplementary material). The results reveal that antitumor activities of curcuminoids are enhanced more by complexation with aluminum than with transition metal ions [26–29].

Table 5. Effect of compounds on Ascites tumor reduction.

Compound	No. of animals with tumor	No. of days survived	Increase in life span (%)
Control	6/6	17.3 ± 1.1	
HL^1	6/6	22.4 ± 1.9	29.5*
HL^2	6/6	30.1 ± 1.5	74.0*
HL^3	6/6	29.2 ± 2.7	68.8*
$[Al(L^1)_3]$	6/6	26.5 ± 1.8	53.2*
$[Al(L^2)_3]$	6/6	35.1 ± 1.7	102.9*
$[Al(L^3)_3]$	6/6	31.5 ± 1.4	82.0*

*$p < 0.001$. Values are means ± SD of six determinations.

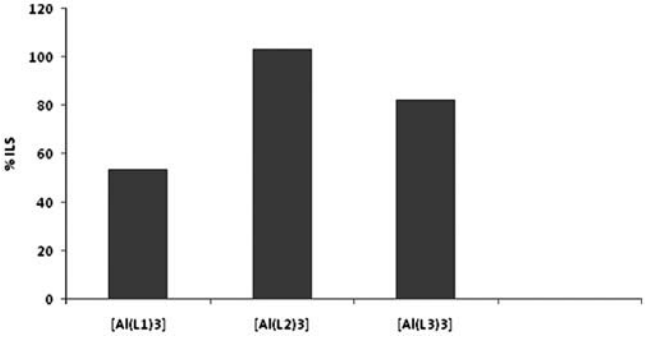

Figure 4. Effect of aluminum complexes of curcuminoids on Ascites tumor reduction.

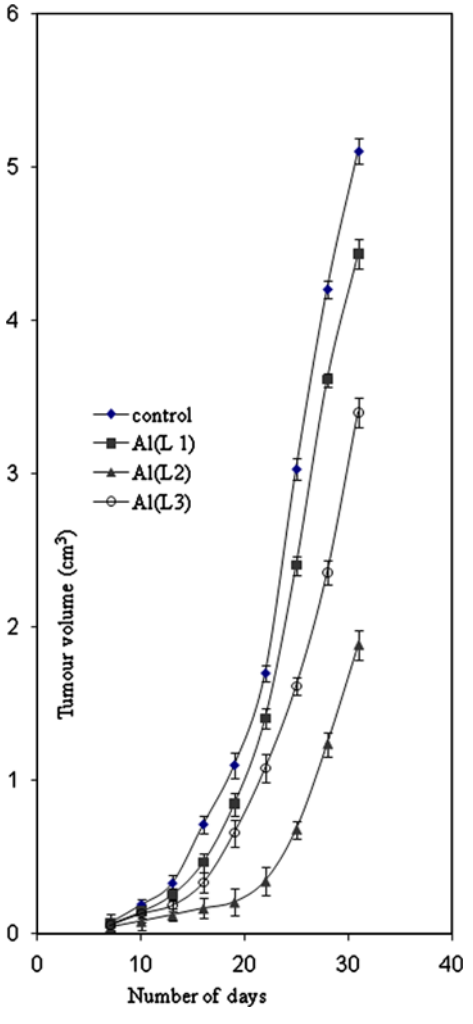

Figure 5. Effect of aluminum complexes of curcuminoids on solid tumor development.

3.2.4. Effect of compounds on solid tumor development. Reductions of solid tumor volume in mice by the administration of compounds (ip) are given in figure 5 and Supplementary material. Compared to free curcuminoids, their respective aluminum(III) complexes are remarkably active in reducing tumor volume in mice. Tumor volumes were, respectively, 5.102, 4.657, 3.390, and 3.885 cm^3 on day 31 for control, HL^1, HL^2, and HL^3. The tumor volumes on day 31 for aluminum complexes of HL^1, HL^2, and HL^3 were, respectively, 4.431, 1.879, and 3.398 cm^3.

4. Conclusion

Three curcuminoid analogues were prepared by condensation between acetylacetone and aromatic aldehydes (benzaldehyde, salicylaldehyde, and 4-ethoxybenzaldehyde) under specified conditions. The analytical and spectral data indicate the existence of the compounds in the intramolecularly hydrogen-bonded keto-enol form. Their aluminum(III) complexes, AlL_3, were synthesized and characterized by UV, IR, ^{1}H NMR, and mass spectral data. In complexes, curcuminoids are monobasic bidentate in which the intramolecularly hydrogen-bonded enolic proton is replaced by Al(III). The compounds were investigated for their possible cytotoxic and antitumor activities. The results clearly reveal that HL^2, with hydroxyl on the phenyl ring, shows largest cytotoxicity on Ehrlich ascites and cultured L929 cells, percentage increase in lifespan and reduction of solid tumor volume in mice. This may be due to the nature of curcuminoid which can yield phenolic structure upon metabolism as well as due to the extended conjugation. Among the compounds studied, HL^1 with unsubstituted benzene ring showed least activity. Complexation with aluminum significantly increased the cytotoxic and antitumor activities of curcuminoids. Aluminum forms stable complexes with curcuminoid analogues and significantly enhances antitumor activity of these compounds, more than their transition metal complexes. This may be due to comparatively higher solubility of aluminum complexes in body fluids than transition metal complexes. Further studies have to be conducted to elucidate the exact mechanism of action.

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References

[1] J.S. Jurenka. *Altern. Med. Rev.*, **14**, 141 (2009).
[2] T. Ak, I. Gulcin. *Chem. Biol. Interact.*, **174**, 27 (2008).
[3] J.L. Funk, J.B. Frye, J.N. Oyarzo, H. Zhang, B.N. Timmermann. *J. Agric. Food Chem.*, **58**, 842 (2010).
[4] S. Chitra, J. Sonia, K.B. Ajaikumar, A.B. Bharat. *Cancer Lett.*, **267**, 133 (2008).
[5] J. Ravindran, G.V. Subbaraju, M.V. Ramani, B. Sung, B.B. Aggarwal. *Biochem. Pharmacol.*, **79**, 1658 (2010).
[6] C.A. Mosley, D.C. Liotta, J.P. Snyder. *Adv. Exp. Med. Biol.*, **595**, 77 (2007).
[7] C.E. Nichols, D. Youssef, R.G. Harris, J. Amitabh. *Arkivoc*, **13**, 64 (2006).
[8] S. Sumathi, P. Tharmaraj, C.D. Sheela, R. Ebenezer. *J. Coord. Chem.*, **65**, 506 (2012).
[9] S.J. Flora. *Oxid. Med. Cell. Longev.*, **2**, 191 (2009).
[10] X. Zhao, T. Jiang, L. Wang, H. Yang, S. Zhang, P. Zhou. *J. Mol. Struct.*, **984**, 316 (2010).
[11] G. Modi. *Der Chem. Sin.*, **2**, 91 (2011).
[12] H. Lissauer, Berliner Klin. *Wochenschrift*, **2**, 403 (1865).
[13] G. Tarchiani, S. Vitale. *Clin. Ter.*, **31**, 101 (1964).
[14] W.A. Collier, F. Krauss. *Krebsforsch*, **34**, 526 (1931).
[15] T.W. Hambley. *Science*, **318**, 1392 (2007).
[16] N.J. Farrer, L. Salassa, P.J. Sadler. *Dalton Trans.*, **48**, 10690 (2009).
[17] R.B. Martin, M. Nicolini, P.F. Zatta, B. Corain. *Aluminium in Chemistry, Biology and Medicine*, 1, Cortina International, Verona (1991).
[18] P. Rubini, A. Lakatos, D. Champmartin, T. Kiss. *Coord. Chem. Rev.*, **228**, 137 (2002).
[19] P.C. Ferreira, A.P. Kde, A.M. Takayanagui, S.I. Segura-Munoz. *Rev. Lat. Am. Enfermagem*, **16**, 151 (2008).
[20] S. Kobayashi, S. Fujiwara, S. Arimoto, H. Koide, J. Fukuda, K. Shimode, S. Yamaguchi, K. Okada, T. Tsunematsu. *Prog. Clin. Biol. Res.*, **317**, 1095 (1989).

[21] S.J. Flora, V. Pachauri. *Int. J. Environ. Res. Public Health*, **7**, 2745 (2010).
[22] S. Daniel, J.L. Limson, A. Dairam, G.M. Watkins, S. Daya. *J. Inorg. Biochem.*, **98**, 266 (2004).
[23] A. Kumar, S. Dogra, A. Prakash. *Behav. Brain Res.*, **205**, 384 (2009).
[24] M. Shirodker, V. Borker, C. Nather, W. Bensch, K.S. Rane. *Indian J. Chem.*, **49**, 1607 (2010).
[25] M. Bouyahyi, T. Roisnel, J. Carpentier. *Organometallics*, **29**, 491 (2010).
[26] V.D. John, K. Krishnankutty. *Appl. Organomet. Chem.*, **20**, 477 (2006).
[27] V.D. John, K. Krishnankutty. *Transition Met. Chem.*, **30**, 229 (2005).
[28] V.D. John, K. Krishnankutty. *Synth. React. Inorg. Met.-Org. Chem.*, **33**, 343 (2003).
[29] V.D. John, G. Kuttan, K. Krishnankutty. *J. Exp. Clin. Cancer Res.*, **21**, 219 (2002).
[30] I. Bremner. *Am. J. Clin. Nutr.*, **67**, 1069S (1998).
[31] V.D. John, K. Krishnankutty. *Main Group Met. Chem.*, **33**, 157 (2010).
[32] K. Krishnankutty, P. Venugopalan. *Synth. React. Inorg. Met.-Org. Chem.*, **28**, 1313 (1998).
[33] K. Krishnankutty, P. Venugopalan. *J. Indian Chem. Soc.*, **75**, 2 (1998).
[34] H.J.J. Pabon. *Rec. Trav. Chim.*, **83**, 237 (1964).
[35] J.M. Caron, M. Bannon, L. Rosshirt, J. Luis, L. Monteagudo, J.M. Caron, G.M. Sternstein. *PLoS ONE*, **5**, e11788 (2010).
[36] L. Walker, M.C. Walker, C.N. Parris, J.R. Masters. *Urol. Res.*, **16**, 329 (1988).
[37] American Cancer Society *CA Cancer J. Clin.*, **33**, 122 (1983).
[38] G. Kuttan, D.M. Vasudevan, R. Kuttan. *Cancer Lett.*, **41**, 307 (1988).
[39] J.R. Anto, K.V. Dineshbabu, K.N. Rajasekharan, R. Kuttan. *Cancer Lett.*, **94**, 74 (1995).
[40] L.J. Bellamy. *The Infrared Spectra of Complex Molecules*, Chapman and Hall, London (1980).
[41] N. Nakamoto. *Infrared Spectra and Raman Spectra of Inorganic and Coordination Compounds*, Wiley, New York, NY (1997).
[42] F. Payton, P. Sandusky, W.L. Alworth. *J. Nat. Prod.*, **70**, 143 (2007).