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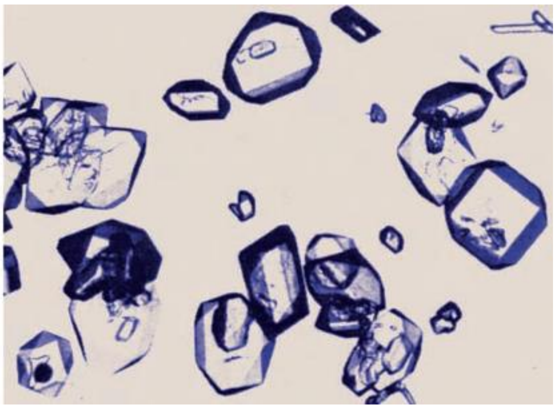
Form I

**References**

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# ANTITUMOUR ACTIVITY OF SOME SYNTHETIC CURCUMINOIDS AND THEIR Al(III) COMPLEXES

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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 anti-inflammatory, anti-oxidant, anti-arthritic and anti-tumour activities. 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 several structurally related compounds. The medicinal importance of many plant chemicals are enhanced by complex formation with various metal ions. Metal complexation of these unsaturated 1,3-diketones lead to dramatic changes in their biochemical properties including antitumour activity. The antitumor activities of natural and synthetic curcuminoids are enhanced by complexation with some transition metal ions even though these metal ions themselves are toxic to animal body.

The curcuminiod analogues (Fig. 1) were prepared by the condensation of aromatic aldehydes with acetylacetone-boric oxide complex in ethylacetate medium in the presence of tri(*sec*-butyl)borate and *n*-butyl amine. Their Al(III) complexes (Fig. 2) were prepared from $Al(NO_3)_3.9H_2O$.

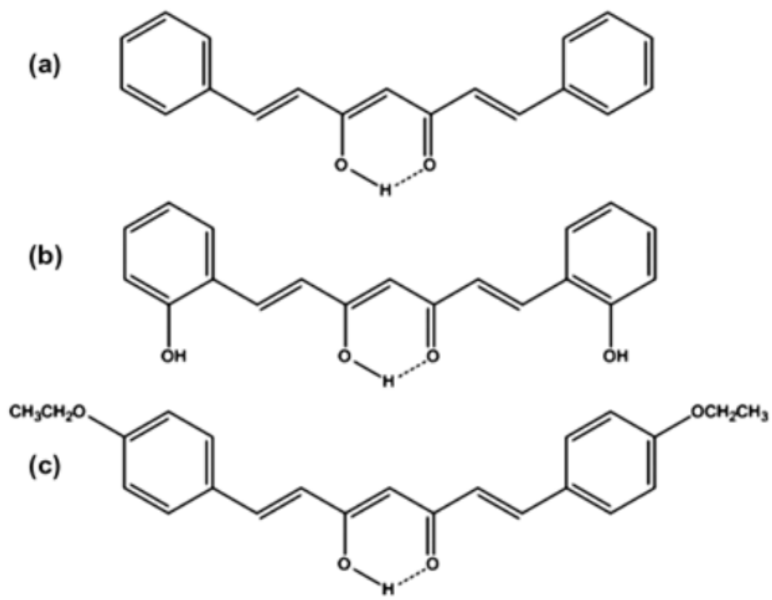


**Fig. 1.** Structure of curcuminoid analogues: (a) 1,7-diphenyl-1,6-heptadiene-3,5-dione ($HL^1$); (b) 1,7-bis(2-hydroxyphenyl)-1,6-heptadiene-3,5-dione ($HL^2$); (c) 1,7-bis(4-ethoxyphenyl)-1,6-heptadiene-3,5-dione ($HL^3$)

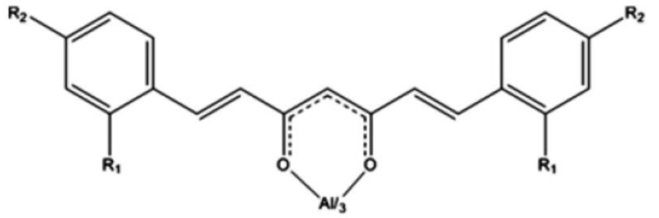


**Fig. 2.** Structure of the aluminium complexes of curcuminoids

*$R_1$* *$R_2$*


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| | | |
|---|---|---|
| $[Al(L^1)_3]$ | H | H |
| $[Al(L^2)_3]$ | OH | H |
| $[Al(L^3)_3]$ | H | $OCH_2CH_3$ |

Ehrlich ascites carcinoma cells were used for *in vitro* cytotoxic studies. The compounds were dissolved in minimum quantity of DMSO which does not enhance cytotoxicity. The tumour cells aspirated from the peritoneal cavity of tumour bearing mice were washed with PBS (phosphate buffered saline). The cell suspension (1 x $10^6$ cells in 0.1 mL) was added to tubes containing various concentrations (1-50 ⌠g/ml) of the compounds and volume was made up to 1 ml using PBS. The mixture was incubated for 3 hours at $37^0$C and the percentage of dead cells were evaluated by trypan blue dye exclusion method. The results indicate that metal chelation enhance the cytotoxicity of compounds considerably. Among the compounds subjected to short term assay the aluminium complex of $HL^2$, with a hydroxyl group in the phenyl ring, is found to be the most active and $HL^1$, which possess unsubstituted benzene ring system, shows low activity.

L929 cells were used for tissue culture studies. The cells (5 x $10^3$ cells/well) were plated in tarzon's 96 well flat bottom titre plates and incubated at $37^0$C in 5% $CO_2$ atmosphere. After 24 hours of incubation various concentrations (1-10 ⌠g/ml) of compounds were added to the wells and incubated for a further period of 48 hours. 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. The results indicate that the aluminium chelates are more cytotoxic than the respective curcuminoids. Compound $HL^1$ is the least active and aluminium complex of $HL^2$ is the most active.

Groups of Swiss albino mice (6 per group) were injected intraperitonially (ip) with Ehrlich ascites tumour cells (1 x $10^6$ cells/animal). The animals were injected (ip) with test compounds (200 ⌠moles/kg body weight) suspended in gum accasia and the injections were continued for 10 days. The mortality rate of mice were noted in each group and the percentage increase in life span (% ILS) of the treated group was calculated using the formula %ILS = [100(T-C)]/C, where T is the mean survival time of treated mice and C is that of control expressed in days. All the compounds when administered intraperitonially (ip) produced significant increase ($p$ <0.001 from normal) in the life span of mice bearing ascites tumours. Aluminium (III) complexes produced a considerable increase in life span of tumour bearing mice compared with that of curcuminoids. The percentage increase in life span (%ILS) of tumour bearing mice was found minimum for $HL^1$ and maximum for aluminium complex of $HL^2$. The results reveal that antitumour activities of curcuminoids are enhanced more by complexation with aluminium than with transition metal ions.

The effect of various compounds on solid tumour 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 other groups were injected (ip) with test compounds (200 ⌠moles/Kg body weight) and the injections were continued for 10 days. Tumour diameter was measured every third day for one month and tumour volume calculated using the formula, $V = 4/3\square r_1 r_2^2$ where $r_1$ and $r_2$ are the minor and major radii respectively. Reductions of solid tumour volume in mice by the administration of


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compounds (ip) show that compared to free curcuminoids their respective aluminium (III) complexes are remarkably active in reducing tumour volume in mice.

The results clearly reveal that $HL^2$, with hydroxyl groups on the phenyl ring, shows the maximum activity towards cytotoxicity on Ehrlich ascites and cultured L929 cells, percentage increase in life span and reduction of solid tumour volume in mice. This may be due to the peculiar nature of curcuminoid analogue 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 aluminium significantly increased the cytotoxic and antitumour activities of curcuminoids. The study suggests that the main group element aluminium forms stable complexes with curcuminoid analogues and significantly enhances antitumour activity of these compounds than in their transition metal complexes. This may be due to the comparatively high solubility of aluminium complexes in the body fluids than the transition metal complexes. Further studies have to be conducted to elucidate the exact mechanism of action.

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# ANTICANCER AND ANTIMICROBIAL ACTIVITIES OF SOME SYNTHETIC NITROGEN HETEROCYCLICS

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