Synthesis and Antiarthritic Study of a New Orally Active Diferuloyl Methane (Curcumin) Gold Complex

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Abstract

Gold(I) complex of composition $[AuL_2]Cl$ with diferuloyl methane (Curcumin) has been synthesised and characterised by elemental analysis, magnetic moment, IR and electronic spectral studies. Antiarthritic studies on rats were also carried out using three parameters: (1) assessment of remission in adjuvant induced polyarthritis assessed by measurement of paw volume, (2) X-ray studies to see the anatomical changes of the affected limb, and (3) the changes in the serum acid phosphatase level during the disease course. The serum gold levels were also determined at different dose levels.

Curcumin has been shown to be a non-toxic anti-inflammatory agent [1–3]. The curcumin gold complex was prepared by mixing curcumin with auric chloride in the ratio of 2:1 in ethanol; the mixture was refluxed for eight hours. On cooling, brown crystals of curcumin–gold complex separated out; these were then dried over P_4O_{10}. The magnetic susceptibility measurements were carried out on a Gouy balance using $Hg[Co(CNS)_4]$ as the calibrating agent. The IR spectra of curcumin and the complex were recorded on a Perkin-Elmer 621 automatic recording spectrophotometer in KBr medium. Elemental analysis of the complex suggests that it has the composition $Au(ligand)_2Cl$. Conductivity of the complex could not be determined due to the poor solubility in all the common organic solvents. The complex is diamagnetic as expected for a d^{10} type system. The electronic spectrum of the complex was recorded in nujol mull on a DMR-21 recording spectrophotometer. Since gold(I) is a d^{10} system, no d–d band was expected. The electronic spectrum of the complex displays two bands at 32 000 and 26 000 cm^{-1}. These bands may be due to charge transfer [4]. IR spectroscopy provided direct information regarding the coordination of ligands. A comparative study of the ligand and the complex suggests that the ligand acts as neutral bidentate. The IR spectrum of the ligand exhibits a band at 3350 cm^{-1}, due to the OH group [5]. On complexation the position of the band remained unaltered, which suggests that no coordination takes place through the OH group. A band at 1730 cm in the ligand may be assigned to C=O (5%). On complexation the position of this band is shifted towards lower wavenumbers. This suggests that the ligand coordinates with the central metal ion through the C=O group. On the basis of IR and electronic spectral studies, the structure of the complex may be assigned as shown in Fig. 1.

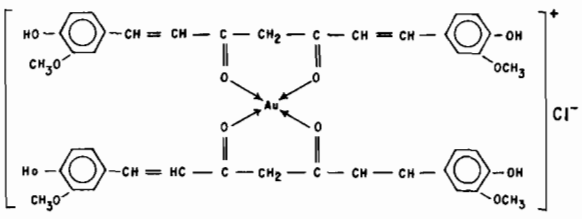

Fig. 1. Structure of the curcumin gold complex.

In the present study, antiarthritic properties of the gold curcumin complex were evaluated by measuring its ability to inhibit swelling in the contralateral paw assessed by measuring the paw volume on day twenty-one. The anatomical changes were compared from the X-ray pictures of the affected limb in rats. The results have been expressed as percent protection and compared with those of acetylsalicylic acid. The results obtained in this animal model (see Table I) indicate that on the 21st day of the injection of adjuvant the gold complex at the dose of 30 mg/kg produced 68.75% inhibition of the paw swelling, while acetylsalicylic acid produced 49.56% protection at 200 mg/kg. However, the same dose of acetylsalicylic acid at 30 mg/kg did not give any protection. X-ray changes of the affected areas show changes in the bone tissue which cannot be accurately assessed only by measuring the volume of

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TABLE I. Effect of Gold Diferuloyl Methane Complex on Adjuvant Induced Polyarthritis on Day 21

Drug	Dose (mg/kg/day)	Percent protection[a]	Increase in serum acid phosphatase level from normal values (%)	Serum gold (μg/ml)
Control	vehicle	0	153.11	
Gold diferuloyal methane	5	15 ($p > 0.05$)	106.65	0.8
Gold diferuloyal methane	10	67.4 ($p < 0.05$)	56.24	1.3
Gold diferuloyal methane	30	68.75 ($p < 0.05$)	53.00	1.8
Acetylsalicylic acid	200	49.56	132.78	

[a]Number of animals in each group = 6.

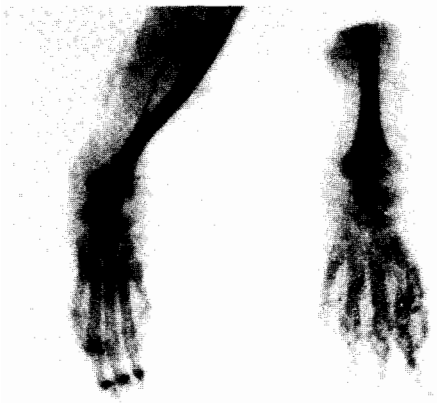

Fig. 2. Controlled tissue swelling, untreated rats day 21.

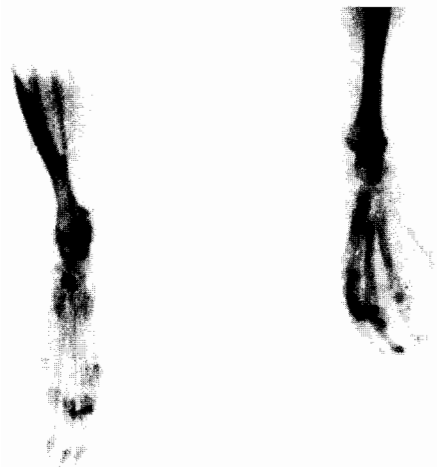

Fig. 3. Drug treated tissue (30 mg/kg).

the locally inflamed site. The X-ray pictures show extensive destructive lesions at the ankle joints and periosteal reactive changes that could be assessed by comparison with pictures of a control animal. Figure 2 shows the control negative wherein surrounding tissue swelling is considerable. There are also destructive lesions in the tarsals and metatarsals. On treatment with gold complex (30 mg/kg), surrounding tissue swelling (Fig. 3) was less.

The probable mechanism of action of the gold curcumin complex can be conjectured from the serum acid phosphatase levels of the treated and untreated groups of animals. Extensive tissue breakdown in adjuvant arthritis is due to the release of a lysosomal enzyme which has a degradative effect on the connective tissue component. Interestingly, it was observed that there was an overall increase of 153% of serum acid phosphatase in the control group of rats compared to the normal rats. The reduction in the gold treated group was very significant as far as serum acid phosphatase levels are concerned. This was not seen in acetylsalicylic acid treated animals. So the mechanisms involved are different for the two drugs. The gold complex probably acts by lysosomal enzyme inhibition.

The serum gold concentration measured by atomic absorption spectrometry shows that the compound is absorbed from the gastrointestinal tract (Table I). However, the levels were not dose-dependent.

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