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Research Article

ANTIOXIDANT STUDIES OF SOME SYNTHETIC CURCUMINOIDS

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ABSTRACT

The antioxidant activity of eight curcuminoid analogues (HL^1 to HL^8) was studied by thiocyanate method. The results revealed that the antioxidant property depends on the nature of aryl substituents and the extent of conjugation present in the compounds. A comparison of the observed antioxidant and reported antitumour activities of these synthetic curcuminoids revealed that compounds having highest antitumour activity also exhibited maximum antioxidant activity.

INTRODUCTION

Curcuminoids are a group of natural phenolic compounds with potent antioxidant properties[1]. Several research groups have recently provided convincing evidences for the antioxidant properties of curcuminoids and turmeric extracts[1,2]. Both turmeric and curcuminoids inhibit generation of potent free radicals like superoxide and hydroxyl radicals[3]. The antioxidant property of curcumin in the prevention of lipid peroxide, a process that generates free radicals, is well recognized[4]. Curcuminoids have been reported as safe and effective antioxidants, and scavenge free radicals at the cost of becoming weak free radicals themselves[5]. The free radicals thus formed do not pose any health hazard. Also, the curcuminoid free radicals, unlike those of synthetic phenolics like BHT and BHA, are short lived which further adds to their safety. In this investigation, the antioxidant activity of some curcuminoid analogues is studied.

Experimenital

***Preparation of curcuminoid analogues**:* The curcuminoid analogues (HL^1–HL^8) were synthesized by the Claisen-Schmidt condensation between acetylacetone and aromatic aldehydes (benzaldehyde, cinnamaldehyde, furfural, salicylaldehyde, *β*-hydroxy-*α*-naphthaldehyde, *p*-methoxybenzaldehyde, *p*-hydroxybenzaldehyde and vanillin) in presence of tri(*sec*-butyl)borate and boric oxide using *n*-butylamine as the condensing agent as reported[6-12].

***Determination of antioxidant activity**:* The thiocyanate method[13] was employed for determining the antioxidant activity of curcuminoids. In this method, the ability of lipid hydroperoxide, formed during the autoxidation of linoleic acid, to oxidise Fe^{2+} into Fe^{3+} was exploited. The sample and linoleic acid in a water-ethanol medium was incubated at 40°C in the dark and the autoxidation was followed at intervals by measuring the absorbance (at 500 nm) of the red colour developed after the addition of ferrous salt and ammonium thiocyanate solutions. As the concentration of Fe^{3+}, and hence absorbance, depends on the extent of lipid autoxidation, the antioxidant activity of the sample can be judged qualitatively from the comparison of absorbance of a control maintained under identical conditions.

A solution (2.53%) of linoleic acid in 99.5% ethanol and 0.05 M phosphate buffer of pH 7 were prepared. Solution (4 mL) of the test compound (2 mg in 99.5% ethanol) was added to a

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solution mixture containing linoleic acid (4.1 mL), phosphate buffer (8 mL) and distilled water (3.9 mL) taken in an Erlenmeyer flask. The mixture was incubated at 40°C in the dark for 7-8 days. At periodic intervals, during the incubation, 100 mL of the mixture was used for antioxidant assay.

The incubated solution (100 mL) was added to a mixture of 75% ethanol (9.7 mL) and 30% NH_4SCN (0.1 mL). Fe^{2+} solution (0.1 mL, 2×10^{-2} M) in 3.5% HCl was then added and after 3 minutes the absorbance of the red colour developed was measured at 500 nm. The antioxidant activity was judged from the decrease in the absorbance compared to the absorbance of a control.

RESULTS AND DISCUSSION

The structure of the curcuminoid analgues[7-12] (Fig. 1) was reported earlier based on various analytical and spectral techniques.

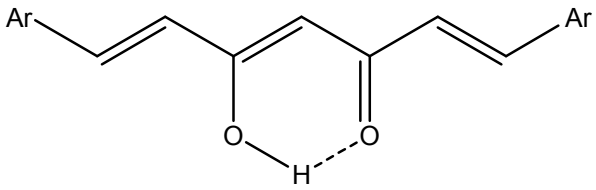

Fig 1 Structure of the curcuminoid analogues; Ar = phenyl (HL^1); styryl (HL^2); 2-furyl (HL^3); 2-hydroxyphenyl (HL^4); 2-hydroxy-1-naphthyl (HL^5); 4-methoxyphenyl (HL^6); 4-hydroxyphenyl (HL^7); and 4-hydroxy-3-methoxyphenyl (HL^8).

The results of the antioxidant activity of curcuminoid analogues obtained are presented graphically (absorbance at 500 nm *Vs* number of days) in Fig. 2. The control is also included in the figure to clarify the extent of activity. Antioxidant activity of the curcuminoid analogues correlates with their ability to scavenge reactive oxygen species.

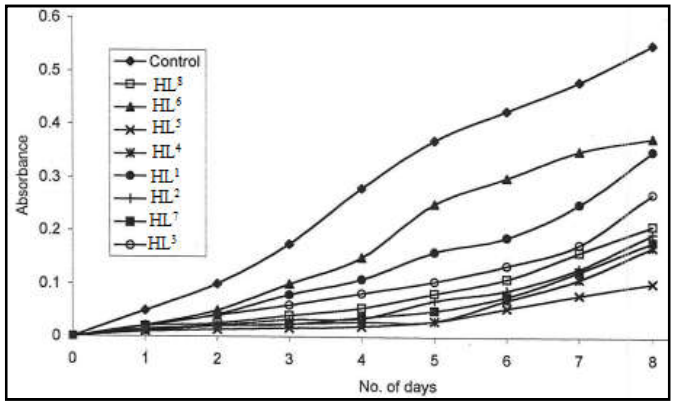

Fig 2 Antioxidant assay of curcuminoid analogues

Among the compounds, highest antioxidant property is shown by HL^5 and the lowest activity by HL^6. The observed order of antioxidant activity is $HL^5 > HL^4 > HL^7 > HL^2 > HL^8 > HL^3 > HL^1 > HL^6$. Since the structural unit in all curcuminoids is the diketo function (predominantly enolised), the variation in activity of the compounds can arise only due to the variation of aryl substituents.

Extended conjugation increased the activity. Thus HL^5 and HL^2 show more activities than HL^1. Presence of –OH group on the aryl ring (in HL^4, HL^5, HL^7 and HL^8) markedly increased the antioxidant activity. Since HL^6 showed least activity, it can be inferred that methoxy group is not a major contributor to the antioxidant activity. An –OH group *ortho* to the olefinic linkage is more favourable for antioxidant behavior than an –OH group in the *para* position. This is evident from the data that HL^7 shows less activity than HL^4.

Our previous studies revealed that the curcuminoid analogues, considered in the present investigation, possess antitumour activities[7-11]. A comparison of the observed antioxidant and reported antitumour activities revealed that the curcuminoid analogues having highest antitumour activity also exhibited maximum antioxidant activity. The reported antitumour activity (reduction in tumour volume in mice) and the observed antioxidant activity of the curcuminoid analogues are given in Fig. 3 and Fig. 4 for comparison. Thus HL^5 and HL^4 which contain –OH group at the *ortho* position of the aryl ring exhibited maximum antioxidant and antitumour activities.

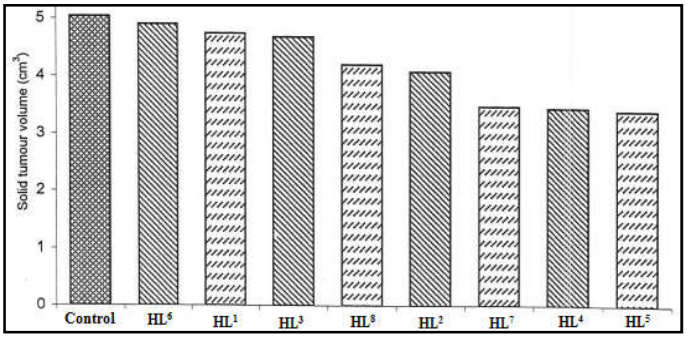

Fig 3 Solid tumour volume on day-31 with respect to control

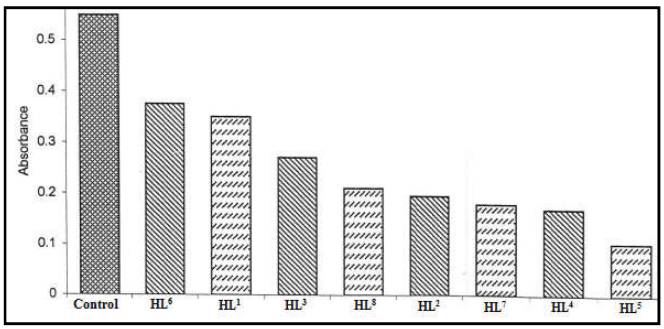

Fig 4 Absorbance on day-8 with respect to control

CONCLUSIONS

The effects of aryl substituents and conjugation on the antioxidant properties of some curcuminoid analogues [Ar = phenyl (HL^1); styryl (HL^2); 2-furyl (HL^3); 2-hydroxyphenyl (HL^4); 2-hydroxy-1-naphthyl (HL^5); 4-methoxyphenyl(HL^6); 4-hydroxyphenyl (HL^7); and 4-hydroxy-3-methoxyphenyl (HL^8)] were studied. Among the curcuminoid analogues with unsubstituted aryl rings, antioxidant activity increased with increase in conjugation. Curcuminoid analoguess with phenolic groups showed maximum antioxidant activity. Among the compounds, highest antioxidant property was shown by HL^5 due to the presence of both phenolic groups and extended conjugation. The observed antioxidant activities follow the order $HL^5 > HL^4 > HL^7 > HL^2 > HL^8 > HL^3 > HL^1 > HL^6$. The results obtained are comparable with the reported antitumour activity of the curcuminoid analogues.

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