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Enhanced anti-inflammatory activity of curcumin, a naturally occurring pigment in turmeric via cyclodextrin complexation

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SUMMARY

Curcumin, a dietary pigment responsible for the yellow color of curry, has been used for the treatment of inflammatory diseases and exhibits a variety of pharmacological effects such as anti-inflammatory, anti-tumor, anti-oxidant, and anti-viral activity. In order to examine the potency of the curcumin in inflammation we used carrageenan induced rat hind paw odema model. As curcumin is practically water insoluble, it is hypothesized that pharmacological activity of curcumin could be improved by enhancing its water solubility. Water soluble complexes of curcumin with cyclodextrins were prepared and screened for greater solubility. Pure curcumin 100 mg/kg body weight along with curcumin complexes equivalent to 100 mg/kg body weight of pure curcumin were tested for the anti-inflammatory activity in Wister rats male rats using carrageenan induced hind paw edema model and compared with that of the reference compound diclofenac sodium at a dose level of 10 mg/kg body weight. Results were statistically analyzed using ANOVA. All the treatment groups showed statistically significant anti-inflammatory activity compared with that of vehicle control and positive control.

Key words: Curcumin; Anti-inflammatory; Carrageenan; Hind paw edema

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used of all therapeutic agents. They are frequently prescribed for long-term treatment of rheumatic musculo-skeletal complaints. The major drawback to anti-inflammatory drug use is the occurrence of gastrointestinal side effects with majority of agents. Curcumin is a natural polyphenol, obtaioned from *Curcuma longa* (Family: Zinziberaceae). It has been used to relieve the pain and inflammation since ancient times in traditional system. Recent extensive research has claimed the curcumin to possess many therapeutic actions including good anti-inflammatory (Arora *et al.*, 1971; Chandra *et al.*, 1972; Mukhopadhyay *et al.*, 1982). Curcumin appears to block synthesis of certain prostaglandins through inhibition of cyclooxygenase and lipoxygenage (Huang *et al.*, 1991; Skrzypczak-Jankun *et al.*, 2000; Wallace *et al.*, 2002). Details of pharmacological activity profile and other aspects have already been published by the group (Kohli *et al.*, 2005).

The most interesting feature of curcumin is that it is devoid of gastrointestinal side effects (ulcerogenic activity) rather it is reported to have anti-ulcer properties (Sinha *et al.*, 1974; Rafatulla *et al.*, 1990). Many pre-clinical trials (Srimal *et al.*, 1971; Srimal

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and Dhawan, 1973; Deodhar *et al.,* 1980) and some clinical trials (Satoskar *et al.,* 1986; Kuttan *et al.,* 1987; Cheng *et al.,* 2001) have revealed that curcumin is safe even up to a dose level of 8.0 g/kg but no formulation is available in the market because of its poor bioavailability (about 60%). Oral absorption of curcumin is dissolution rate limited due to very low aqueous solubility and rapid biotransformation. Photodecompositions in solid as well as solution form further contribute in poor bioavailability of curcumin (Tonnesen *et al.,* 1986).

Cyclodextrins have been successfully used to enhance either solubility or stability or both of the drugs of plant origin like theophylline (Ammar *et al.,* 1996), camptothecin (Cheng, 2003) pilocarpine (Aktas *et al.,* 2003) psoralen (Vincieri *et al.,* 1995) paclitaxel (Sharma *et al.,* 1995), tretinoin (Brisaert and Plaizier-Vercammen, 2000) acitretin (Liu, 2003) rutin (Miyake, 2000), artemisinin (Wong and Yuen, 2001, 2003; Illapakurthy, 2003; Usuda *et al.,* 2005), digoxin (Uekama *et al.,* 1981; He, 2004), quercetin (Pralhad and Rajendrakumar, 2004) etc thereby increasing the biological activities and therapeutic values of the natural compounds. In this paper we hypothesized that cyclodextrin complexes of curcumin may improve its stability, solubility and bioavailability thereby pharmacological activity. We prepared and investigated the anti-inflammatory effect of pure curcumin, curcumin-cyclodextrin complexes and compared with that of the diclofenac sodium which was used as standard anti-inflammatory drug.

MATERIAL AND METHODS

Materials

Curcumin was purchased from Loba chemicals (Banglore, India.). Dimethyl β-cyclodextrin (DIMEB) was purchased from Sigma Aldarich, Chem. U.S.A. Other cylodextrins like α-CD, β-CD and γ-CD were obtained from S. D. Fine Chemicals (India). All other compounds and solvents used in this study were of analytical-reagent grade.

Preparation of inclusion complexes of curcumin

The inclusion complexes of curcumin with various cyclodextrins (α-CD, γ-CD and dimethyl β-CD) were prepared in a 1.1 molar ratio (1: 2 molar ratio was used in case of curcumin. β-CD) using various methods viz: grinding, kneading and freeze drying (Baboota and Agarwal, 2003; Rawat and Jain, 2003).

Aqueous solubility determination of the solid complexes

Solubility studies of curcumin were done by the method described by Higuchi and Conners (1965) with slight modification. Excess amount of pure curcumin and curcumin complexes were kept in amber coloured bottles containing 10 ml of distilled water and stirred on thermostated mechanical shaker (25°C) for 5 days. Suspensions were filtered through 0.45 μm filter, diluted adequately (20 times, except DIMEB complexes which needed 200 times dilution) and analyzed spectrophotometrically at 430 nm. Solubility of curcumin was calculated by using straight-line equation.

Animals

Wistar male albino rats weighing 190 - 210 g, supplied by the Central animal House facility of Jamia Hamdard New Delhi (Registration No. 173/CPCSEA) were used in the study. Animals were kept under laboratory standard conditions on a 12 h light/ dark cycle with light from 8: 00 AM to 8: 00 PM, in a temperature controlled room (22 ± 1°C) with a relative humidity of 55 ± 5%. Solid rodent chow (Amrut rat and mice feet, Pune India) and tap water were given ad libitum. After 3 days of acclimation under these conditions, experiments were performed according to the protocol approved by the Institutional Animal Ethics Committee (IAEC) of Jamia Hamdard University and Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Anti-inflammatory activities of the curcumin and curcumin complexes in Wistar Albino rats

Anti-inflammatory activity was performed using

Table 1. Aqueous solubility of curcumin and curcumin complexes

Type of complex	Solubility of curcumin (μg/ml)				
	Curcumin	Curcumin-α-CD complexes	Curcumin-β-CD complexes	Curcumin-γ-CD complexes	Curcumin-dimeb complexes
PM	1.29	75.1	69.4	48.6	930.1
KN	-	39.4	51.96	52.2	1290.4
FD	-	41.04	43.01	60	1930.1

PM: Physical mixture; KN: kneaded complex; FD: freeze-dried complex.

carrageenan induced rat hind paw edema model (Winter *et al.,* 1962). Wistar Albino male rats were divided into seven different groups each containing six rats. Acute inflammation was produced by injecting 0.1 ml of 1% w/v carrageenin solution in the subplantar region of the rat right hind paw. Drugs were administered by oral route as suspension in 1% w/v of aqueous sodium carboxymethylcellulose (Na CMC), one hour prior to the carrageenan injection. Group I received vehicle control, group VII received diclofenac sodium as positive control and other groups received different treatments. Treatment schedule is given in the Table 1. The paw volume was measured immediately and 4 h after the injection of carrageenin by using digital plethysmometer.

Data analysis

All treatment groups were analyzed by one way parametric One-way analysis of variance (ANOVA) using Graph pad InStat software Demo version downloaded from the site www.graphpad.com. ANOVA tests whether the mean of a dependent variable (% inhibition in paw volume) differs among three or more treatment groups (independent variables). Here we tested whether % inhibition in paw volume differs between a control group and six treatment groups in question. Pair wise comparisons for the drug-treated groups to the vehicle control group as well as multiple comparisons between treated groups were then performed using Tukey test.

RESULTS

Solubility of curcumin

Curcumin is reported to be practically insoluble in water, its saturated solubility in distilled water at room temperature was found to be 1.29 μg/ml. Inclusion complex formation of curcumin greatly enhanced the aqueous solubility up to 60, 54, 46 and 1500 folds by α-, β-, γ- and dimethyl β-cyclodxtrin respectively. Aqueous solubility of pure curcumin and its inclusion complexes (PM-physical mixture, KN-kneaded complex and FD-freeze-dried complex) with various cyclodextrins (α-CD, β-CD, γ-CD and DIMEB) is given in Table 2.

Anti-inflammatory activity

Anti-inflammatory activity of curcumin and curcumin complexes was studied using digital plethysmometer.

Table 2. Treatment groups with dosing schedule

Group No.	No. of rats	Drug/Treatment	Oral Dose
I	6	Vehicle control	-
II	6	Pure curcumin	100 mg/kg body weight
III	6	Curcumin-α-CD complex	Equivalent to 100 mg/kg body weight of curcumin
IV	6	Curcumin-β-CD complex	Equivalent to 100 mg/kg body weight of curcumin
V	6	Curcumin-γ-CD complex	Equivalent to 100 mg/kg body weight of curcumin
VI	6	Curcumin-DIMEB complex	Equivalent to 100 mg/kg body weight of curcumin
VII	6	Diclofenac sodium	10 mg/kg body weight

Table 3. Change in mean paw volume by various treatments

Group No.	Mean initial paw volume at 0 h (mm) (± S.D.) n = 6	Mean paw volume 4 h after treatments (mm) (± S.D.) n = 6	Mean change in paw volume 4 h after treatments (mm) (± S.D.)
I	1.69 (± 0.332)	2.50 (± 0.354)	0.82 (± 0.074)
II	1.63 (± 0.326)	2.1 (± 0.256)	0.56 (± 0.059)
III	1.58 (± 0.268)	2.04 (± 0.214)	0.456 (± 0.070)
IV	1.56 (± 0.356)	1.98 (± 0.189)	0.416 (± 0.045)
V	1.54 (± 0.372)	1.93 (± 0.248)	0.393 (± 0.042)
VI	1.71 (± 0.338)	1.90 (± 0.319)	0.190 (± 0.036)
VII	1.65 (± 0.329)	1.91 (± 0.326)	0.261 (±0.054)

Group II: vs I^{***}, III^{ns}, IV^{**}, V^{***}, VI^{***}, VII^{***}. Group III: vs I^{***}, IV^{ns}, V^{ns}, VI^{***}, VII^{***}. Group IV: vs I^{***}, V^{ns}, VI^{***}, VII^{***}. Group V: vs I^{***}, VI^{***}, VII^{**}. Group VI: vs I^{***}, VII^{ns}. Group VII: vs I^{***}. *P* Values: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ & Ns: Not significant- $P > 0.05$. F ratio: 80.86, Degree of freedom: 41

Basal, after treatment and net change in paw volumes as mean ± SD (n = 6) are given in Table 3. Percentage inhibition of edema was calculated by the formula given below:

$$\% \text{ Inhibition} = \frac{\text{Volume}_{\text{control group}} - \text{Volume}_{\text{treated group}}}{\text{Volume}_{\text{control group}}} \times 100$$

$$\% \text{ Inhibition} = 1 - \frac{\text{Volume}_{\text{treated group}}}{\text{Volume}_{\text{control group}}} \times 100$$

$$\% \text{ Inhibition} = \left[1 - \frac{A - x}{B - y}\right] \times 100$$

Where

A: Mean volume of the treated rats after administration of the carrageenin

X: Mean volume of the treated rats before administration of the carrageenin

B: Mean volume of control rats after administration of the carrageenin

y: mean volume of control rats before administration of the carrageenin

A graph showing comparative inhibition of edema was plotted as shown in Fig. 1. Pure curcumin caused an inhibition of 32.03% whereas curcumin complexes inhibited edema to a greater extent. Maximum of 77.38% of inhibition was obtained by curcumin-dimeb freeze-dried product.

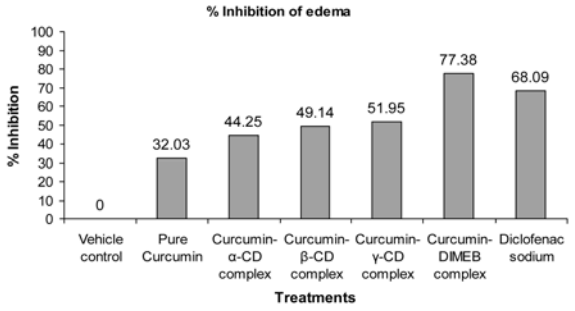

Fig. 1. Inhibition of rat paws edema by curcumin and complexes.

Statistical analyses

All the treatment groups showed statistically significant difference*** when compared to the vehicle control ($P < 0.001$). Among the treatment groups, groups II always showed significant differences*** ($P < 0.001$) except with group III^{ns} ($P > 0.05$). Groups III always showed significant differences*** ($P < 0.001$) except with group II^{ns}, IV^{ns} &V^{ns} ($P > 0.05$). Group IV is not significantly different from group V^{ns} ($P > 0.05$). Group VI & VII always showed significant differences*** when compared to any group ($P < 0.001$) except when compared with eachother^{ns} ($P > 0.05$). F ratio (between treatments variation divided by within treatments variation) of 80.86 for a total degree of freedom of 41 [between treatments (6) + within treatments (35)] indicated significant differences among groups.

DISCUSSION

This study is a part of development and evaluation of oral dosage form of curcumin. The primary mission of these studies was developing the pharmaceutical formulation of a curcumin, a naturally occurring pigment. With regard to the mode of anti-inflammatory action, curcumin exhibits a diverse array of metabolic, cellular, and molecular activities including inhibition of arachidonic acid formation and its further metabolism to eicosanoids. Studies from our laboratory have demonstrated that dietary curcumin significantly inhibits phospholipase A2 in colonic mucosa and tumors leading to the release of arachidonic acid from phospholipids, alter COX and LOX activities, and modify PGE2 levels. Several lines of evidence also indicate that the mechanism of action of curcumin is not limited to PG inhibition (Rao *et al,* 1995). Various pre-clinal and clinical studies have been done but with a very heavy dose of levels of turmeric or curcumin ranging from 200 - 8,000 mg/ day that might be either due to the low potency or low bioavalibility of curcumin or both. In this study low dose level of curcumin was used expecting that the cyclodextrin complexation may enhance the aqueous solubility of curcumin thereby increased activity. Very promising results were obtained in the present study as hypothesized. The solubility of curcumin was enhanced up to 1,500 folds thus increased activity was observed. Recently Han *et al.,* 2004 prepared inclusion complexes of curcumin with beta CD to enhance solubility and bioavaliability of curcumin but solubility of inclusion compound is 10 times than curcumin (Han *et al.,* 2004). Furthermore solid dispersions of curcumin in different ratios with PVP were prepared by spray drying. To overcome the solubility and bioavailability problems of the curcumin. Solid dispersions showed complete dissolution that might aid in improving bioavailability and dose reduction of the drug. (Paradkar *et al,* 2004).

Kaminaga *et al.* (2003) studied *Catharanthus roseus* cell suspension cultures that converted exogenously supplied curcumin to a series of glucosides, none of which has been found in nature so far. The water solubility of curcumin-4',4"-O-beta-D-digentiobioside was 20 million-fold higher than that of curcumin (Kaminaga *et al.,* 2003). Other methods to enhance bioavailability of curcumin include use of the bioenhancers. Shobha *et al.* (1998) have done one such study. They evaluated the effect of piperine, a known inhibitor of hepatic and intestinal glucuronidation, on the bioavailability of curcumin in rats and healthy human volunteers when curcumin (2 g/kg) was given alone to the rats, moderate serum concentration were achieved over a period of 4 h. Concomitant administration of piperine (20 mg/kg) increased the serum concentration of curcumin for a short period of 1 - 2 h post drug and the bioavailability was increased by 154%. (Shobha *et al.,* 1998).

NSAIDs are usually ulcer producing and they cause gastrointestinal side effects more or less. Curcumin is devoid of such side effects rather it is reported to have ulcer-healing property (Sinha *et al.,* 1974; Rafatulla *et al.,* 1990). A phase II clinical trial aiming effect of the long turmeric (*Curcuma longa Linn)* on healing of peptic ulcer was done by Prucksunand *et al.* (2001). After 4 weeks of treatment (600 mg turmeric five times a day) ulcers were ansent in 48% or 12 cases (Duodenal ulcer 9, Gastric ulcer 3). 18 cases (Duodenal ulcer 13, Gastric ulcer 5) had absence of ulcer after 8 weeks of treatment. (Prucksunand *et al.,* 2001). Some earlier reports of ulcer due to use of curcumin (Gupta *et al.,* 1980), produced controversy that warranted the effect of curcumin along with turmeric on the ulcers.

In the present study bioavailability of the prepared curcumin complexes could not be done due to time constraints therefore in near future bioavailability study of the curcumin and curcumin complexes will be observed. Furthermore ulcer healing property of curcumin and turmeric will be compated. In conclusion the prepared curcumin complexes showed a promising results and the same could be exploited for the industrial, purposes in future.

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