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SYNTHESIS AND SCREENING OF ANTIDIABETIC ACTIVITY OF SOME NOVEL CURCUMIN ANALOGUES

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ABSTRACT

Curcumin is a major constituent of turmeric. It possesses divergent pharmacological activities like anti inflammatory, antioxidant, anticancer, anti HIV, hepatoprotective, and anti diabetic activities etc. Curcumin structural analogues were synthesized and reported to possess same or superior activity compared to the Curcumin. Analogues were synthesized using different aromatic substituted aldehydes and they were characterized using spectral data (FTIR, NMR). All the synthesised compounds were screened for anti diabetic activity. From all the six compounds synthesized, compound II and compound III showed highly significant activity than curcumin and are comparable to standard drug glibenclamide. From the six compounds synthesized, four compounds I, II, III, and VI showed superior in antidiabetic activity compared to curcumin and other two compounds IV and V are inferior in antidiabetic activity compared to curcumin. Compound II was equal in activity compared to the standard drug glibenclamide.

KEYWORDS

Curcumin, NCE, analogues, synthesis, antidiabetic activity.

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INTRODUCTION

Curcumin (diferuloyl methane; 1, 7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1, 6-diene-3, 5-dione) is a major constituent found in the spice turmeric, which is derived from the rhizomes of Curcuma longa L. It is commonly used as a dietary spice and colouring agent in cooking and is used as an herb in traditional Indian and Chinese medicine. Curcumin possesses diverse pharmacological effects including anti-inflammatory, antioxidant, anticancer, antidiabetic, antirheumatic, angiogenic, antifertility, antiviral and anti-infectious activities and wound healing properties[1]. Despite curcumin's multiple medicinal benefits, low oral bioavailability of curcumin continues to be highlighted as a major challenge for its therapeutic use. Lower serum and tissue levels of curcumin are observed irrespective of the route of administration due to extensive intestinal and hepatic metabolism and rapid elimination thus restraining curcumin's bioavailability[2,3,4]. Curcumin is also found to be photo-sensitive and requires careful handling. During the last decade, synthetic modifications of curcumin, which were aimed at enhancing its bioactivities, have been intensively studied. Anticancer activities[5], antioxidant of structural analogues of curcumin were found to be more potent than that of curcumin.

Diabetes that is a most dreadful disease affecting 40.9 million people in India and more than 250 million people around the world have diabetes. This total is expected to rise to 380 million within 20 years. Each year a further 7 million people develop diabetes. Long term diabetes leads to other complications like retinopathy, diabetic nephropathy, diabetic neuropathy, atherosclerosis, colon cancer etc. In experimental studies to examine the potential beneficial effects of curcumin against diabetes, curcumin has been shown to reduce hyperlipidemia[6], delay the development of cataract[7], ameliorate renal lesions[8], and reduce the cross-linking of collagen[9] in a streptozotocin-treated diabetic animal model. Curcumin has also been shown to lower blood glucose levels in type 2 diabetic KK-Ay mice[10] and streptozotocin-treated rats[11]. In this study we have synthesized new curcumin analogues so as to overcome the problems associated with curcumin. After synthesis, the solubility of the compounds in a variety of solvents and their stability were determined. Further, the synthesized curcumin derivatives were evaluated for their antidiabetic activity in alloxan induced diabetic rat model.

MATERIALS AND METHODS

Alloxan was procured from Sigma Aldrich, Germany. Glibenclamide was procured from Alka Pharmaceuticals, Hyderabad. 3- hydroxy benzaldehyde and 4- hydroxy benzaldehyde were procured from Lenoid Chemicals Pvt Ltd, Bangalore . 4- Methyl benzaldehyde was procured from Spectrochem Pvt Ltd, Mumbai. 4-chloro benzaldehyde was procured from Himedia Laboratories Pvt Ltd, Mumbai. Salicyladehyde was procured from Otto Kemi, Mumbai. Para–dimethyl amino benzaldehyde was procured from Loba Chemicals Pvt Ltd. Dimethyl formamide, acetyl

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acetone, diethanolamine, methanol, silica column gel, n- hexane, ethyl acetate, benzene and ethanol were procured from Finar Chemicals Ahmedabad. Glycerol, propylene glycol, PEG 400, and PEG 600 were procured from Qualikems fine Chemicals Pvt Ltd, New Delhi.

***Synthesis and characterization of curcumin derivatives*:**

Synthesis of curcumin derivatives was achieved as depicted in the scheme 1 Fig. (**1**)[12]. Two different methods, conventional procedure as well as microwave assisted procedure were used for the synthesis of selected curcumin analogues.

Conventional Procedure:

A mixture of acetyl acetone (0.01 moles), substituted aromatic aldehyde (0.02moles), boric acid (0.01moles) dissolved in dimethyl formamide (DMF; 10-15 ml), were taken into a round bottom flask, and few drops of diethanolamine and acetic acid (1:1) mixture was added drop wisely. The mixture was then refluxed in a mantel for 16 hours at 150 ^{0}C temperature. The reaction was monitored by TLC (Thin Layer Chromatography) for the confirmation of the product. After 16hrs of reflux the reaction mixture was poured into a 10% acetic acid solution and stirred for one hour to get a solid mass. Thus obtained mass was filtered and washed with water. This crude drug was purified and separated by column chromatography using 60-120 mesh TLC grade silica gel. After synthesis, the products were characterized and structures were confirmed using NMR and IR.

Microwave Method:

A mixture of acetyl acetone (0.01 mole), substituted aromatic aldehyde (0.02 moles), boric acid (0.01 mole), in dimethyl formamide (5 ml of DMF), and few drops of diethanolamine and acetic acid(1:1)mixture was taken into a reaction vessel and irradiated under microwave for 6-8 minutes at 640 watts at a pulse rate of 10 seconds. From the reaction mixture, the compounds were obtained as previously mentioned in the conventional procedure.

Preformulation

Two preformulation parameters, solubility analysis and photostability were investigated.

Solubility analysis:

The solubility of the synthesized curcumin derivatives were determined by adding 5 ml of the respective compound solutions (in methanol, 10 mg/ml) to the different buffer solutions like pH 1, pH 5.5, pH 7.4 and pH 10 (50ml). The samples were protected by wrapping the conical flasks with aluminium foil. Samples were shaken continuously for 24 hours using a rotary shaker. After 24hrs samples were filtered, and the absorbance of the filtrate was noted at 425nm using UV-visible spectrophotometer. Solubility was determined from the respective standard graphs of the synthesized compound. Solubility of the compounds was also determined in the solvents like glycerol, propylene glycol, PEG 400, PEG 600, methanol and ethanol.

Photostabity of synthesized compounds

10µg/ml methanolic solutions of the compounds were prepared. This solution was taken in 6 test tubes for each compound in each having 10ml with the concentration being 10µg/ml. 3 test tubes were wrapped with aluminium foil and the other 3 test

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tubes were kept unwrapped. The stability was subsequently determined after measuring the concentration of the samples; absorbance's of these test tubes were taken every 24 hrs for 3days and analyzed at 425nm using UV-visible spectrophotometer.

Antidiabetic activity:

Experimental animals and research protocol approval

Male wistar rats (150–180g) were purchased from Mahaveer enterprises, Hyderabad. Animals were maintained in an air-conditioned room at 22 ± 2 ^{0}C and relative humidity of 45–55% under a 12h light: 12 h dark cycle. The animals had free access to standard food pellets and water was available ad libitum. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) of Vaagdevi College of Pharmacy, Warangal, (Registration No: 1047/ac/07/CPCSEA) and constituted in accordance with the rules and guidelines of the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA), India.

Induction of experimental diabetes and determination of the serum glucose level

Rats were deprived from food for 16 hours (fasted state) before the induction diabetes. Diabetes was induced in male wistar rats by a single intraperitoneal injection of aqueous alloxan monohydrate (80 mg/kg) solution and the serum glucose level determined by the glucose oxidase peroxidase method. The rats showing a serum glucose level above 300 mg/dl (diabetic state) were selected for this study. Blood samples from the experimental rats were collected by retro-orbital plexus technique using heparinised capillary glass tubes. The collected blood samples were centrifuged at a speed of 7000 rpm for 15 min to get serum. Ten microliters of serum and 1ml of working reagent (GOD/POD) were mixed and incubated for 15 min at 37^{0}C. The UV–VIS spectrophotometer (Elico SL 120) reading was adjusted to 0 by measuring the absorbance of blank (distilled water). The absorbance of sample (As) and standard A_{std} provided by manufacturer were measured against blank at 505 nm [13].

Glucose was estimated by using the formula:

$$\text{Glucose (mg/dl)} = \frac{\text{As}}{\text{Astd}} \times 100$$

Where as As = sample reading; Astd = standard reading.

Effect of Curcumin derivatives on serum glucose levels in alloxan induced diabetic mice:

The selected rats were divided into 10 groups (n =3), viz

1. Group I— Alloxan (80 mg/kg, Diabetic control),
2. Group II— Alloxan + Glibenclamide (10mg/kg),
3. Group III— Alloxan + Vehicle (CMC 1%, 0.5ml/rat),
4. Group IV— Alloxan + Curcumin (100mg/kg),
5. Group V— Alloxan + Compound (**1**) (100 mg/kg),
6. Group VI— Alloxan + Compound (**2**) (100 mg/kg)

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7. Group VII— Alloxan + Compound (**3**)I (100 mg/kg),
8. Group VIII— Alloxan + Compound (**4**) (100 mg/kg),
9. Group IX— Alloxan + Compound (**5**) (100 mg/kg),
10. Group X — Alloxan + Compound (**6**) (100 mg/kg).

All compounds were given orally while alloxan was given intraperitoneally. Rats were fasted overnight before the commencement of the study. The study involves the determination of serum glucose levels at 0, 1, 2, 4, 6 and 8 hours after administration of all compounds.

Statistical analysis

Data was expressed as Mean± S.E.M. and statistical analysis was carried out by one-way ANOVA with Student- Newmann- Keuls test performed using GraphPad Prism windows 5.02 for Windows Vista™ BASIC, GraphPad Software, San Diego, California, USA, www.graphpad.com. *p* value was considered significant when <0.05.

RESULTS AND DISCUSSIONS

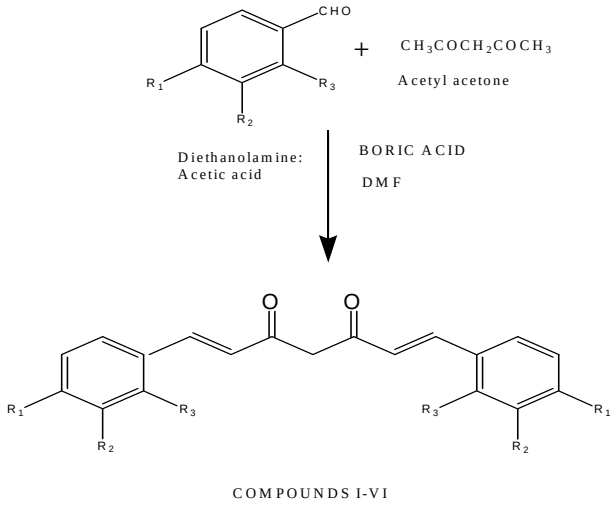
Synthesis

Curcumin derivatives were successfully synthesized using above scheme 1 (Fig. (**1**)) by both conventional and microwave assisted synthesis. The synthesized compounds were purified by column chromatographic techniques using silica gel G as column packing material. Mobile phase compositions used in the purification process are described in Table 1:

Figure 1

Scheme for the synthesis of Novel Curcumin Analogues

SCHEME 1:



COMPOUNDS I-VI

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COMPOUND	R_1	R_2	R_3	REFLUXING TIME(HOURS)
I	H	H	OH	16
II	Cl	H	H	26
III	$N(CH_3)_2$	H	H	16
IV	CH_3	H	H	24
V	H	OH	H	26
VI	OH	H	H	22

Table 1

List of Mobile phase compositions used for purification of Novel Curcumin Analogues

Compound code	Mobile Phase 1 (n- hexane: Ethyl acetate) (in liters)	Mobile Phase 2 (Benzene:Methanol) (in liters)
I	88:12(1)	50:50(0.7)
II	88:12(1.2)	50:50(0.5)
III	75:25(0.5)	50:50(1)
IV	88:12(1)	50:50(0.7)
V	75:25(1.2)	50:50(0.5)
VI	70:30(1.5)	50:50(0.8)

Spectral data (FTIR, NMR) confirmed that the proposed structural analogues were synthesized.

NMR spectral data of compound (**1**)[(1, 7-bis-(2-hydroxyphenyl)-hepta-1, 6-diene-3, 5-dione)] as follows: 9-9.3(s, 2H, Ar-OH); 7.1-7.4(m, 8H, Ar);6.2(d, 2H, HC=CH); 4.8(d, 2H, HC=CH); 3.1-3.5(s, 2H, CH_2)

NMR spectral data of compound (**2**) [(1, 7-bis-(4-chlorophenyl)-hepta-1, 6-diene-3, 5-dione)] as follows: 7.1-7.3(m, 8H, Ar); 5.7(d, 2H, HC=CH); 4.7(d, 2H, HC=CH); 3.6-3.9(s, 2H, CH_2)

NMR spectral data of compound (**3**) [(1, 7-bis-(4-(N, N- dimethyl) phenyl)-hepta-1, 6-diene-3, 5-dione)] as follows: 7.6-7.8(m, 8H, Ar); 6.1(d, 2H, HC=CH); 4.9(d, 2H, HC=CH); 3.3(s, 2H, CH_2); 2.2(s, 12H, $N(CH_3)_2$)

NMR spectral data of compound (**4**) [(1, 7-bis-(4-methylphenyl)-hepta-1, 6-diene-3, 5-dione)] as follows: 7.5-7.7(m, 8H, Ar); 5.9(d, 2H, HC=CH);

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5.3(d, 2H, HC=CH); 3.4(s, 2H, CH_2); 2.3(s, 6H, CH_3)

NMR spectral data of compound (**5**) [(1, 7-bis-(3-hydroxyphenyl)-hepta-1, 6-diene-3, 5-dione)] as follows: 8.8-9.0(s, 2H, Ar-OH); 7.6-7.8(m, 8H, Ar); 6.0(d, 2H, HC=CH); 5.3(d, 2H, HC=CH); 3.5-3.9(s, 2H, CH_2)

NMR spectral data of compound (**6**) [(1, 7-bis-(4-hydroxyphenyl)-hepta-1, 6-diene-3, 5-dione)] as follows: 9.3-9.4 (s, 2H, Ar-OH); 7.3-7.5(m, 8H, Ar); 6.2(d, 2H, HC=CH); 4.7(d, 2H, HC=CH); 4.0(s, 2H, CH_2).Melting point of the compounds were determined using melting point apparatus. Percentage yield was calculated. Values were showed in **Table (2).** The percentage yield was more for the microwave assisted synthesis.

Table 2

Physical and spectral data of curcumin structural analogues

Compound code	MF	Melting Point (^{0}C)	% Yield		IR data
			Conventional procedure	Microwave Method	
I	$C_{19}H_{16}O_4$	184-190	50.08	53.24	>C=O (1728.22), >C=C< (1664.57), >C-H(3061.03), -OH (3612.22), 752.2 for Ortho substitution in the aromatic ring
II	$C_{19}H_{14}O_2Cl_2$	150-156	50.43	56.84	>C=O (1665.98), >C=C< (1548.14), >C-H(3010.13), C-Cl (648.14)
III	$C_{23}H_{14}O_2N_2$	134-140	77.62	87.65	>C=O (1698.98), >C-H(3012.64), C-N (1187.49), -C-C- aromatic (1513.86), 845.57 for Para substitution in the aromatic ring
IV	$C_{21}H_{20}O_2$	110-114	41.25	61.12	>C=O (1685.14), >C-H(3142.60),), -C-C- aromatic (1598.57), 845 for Para substitution in the aromatic ring
V	$C_{19}H_{16}O_4$	234-238	60.84	65.84	>C=O (1691.52), >C-H(3007.64), -OH (3633.59),), -C-C- aromatic (1513.03), 791.53 for Meta substitution in the aromatic ring
VI	$C_{19}H_{16}O_4$	172-176	48.7	54.65	>C=O (1688.73), >C-H(3053.77), -OH (3369.80), -C-C- aromatic (1589.60), 824.65 for Para substitution in the aromatic ring

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Solubility and Photo stability

Standard graphs of the respective compounds were plotted in methanol at different concentrations with R^2 value of 0.99. Solubility and photo stability of the synthesized compounds were determined by the above mentioned procedures and the data was shown in Table 3 and Table 4. Solubility of the synthesized compounds in various solvents was determined (**Table 3).** Solubility of the synthesized compounds in pH 10 was high compared to the other pH solutions. All the compounds were unstable at the pH 10, and the first three compounds were also unstable at pH 1.

Table 3:

Solubility and stability data of Curcumin derivatives

Compound / pH		I	II	III	IV	V	VI
1	Solubility (µg/ml)	146	398	60	28.46	56.48	101.152
	Stability (Color)	changed	Changed	Changed	No Change	No Change	No Change
5.5	Solubility (µg/ml)	17	18.2	6.7	82.307	150.54	118.94
	Stability (Color)	No change	No change	No change	No change	No change	No change
7.4	Solubility (µg/ml)	78	23.25	7.1	114.61	191.428	167.894
	Stability (Color)	No change	No change	No change	No change	No change	No change
10	Solubility (µg/ml)	230	19.2	9	860.384	595.45	833.157
	Stability (Color)	changed	Changed	Changed	Changed	Changed	Changed

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Table 4

Solubility of curcumin derivatives in various solvents in µg/ml

Solvent	I	II	III	IV	V	VI
Methanol	0.9		0.33	5.5	29	15.6
Ethanol	0.6	1.3	0.714	3.33	11.5	38.2
Propylene glycol	1.32	1.10	0.666	-	9.9	3.3
PEG 400	1.5	0.8	1.11	3.33	5.1	1.5
PEG 600	1.6	1	1.428	2.857	1.66	1.1
Glycerol	0.65	0.45	0.333	-	0.333	0.27

Anti diabetic activity

Alloxan injection produced hyperglycaemia in all animals. The single dose administration of the glibenclamide, curcumin and the synthesized compounds to diabetic animals significantly reduced the glucose serum glucose levels at 1, 2, and 4 hours. The standard drug glibenclamide produced maximum activity within 4 hours (reduced initial serum glucose levels up to 67 %). The data is shown in **Table 5** and **Fig 2** represents the effect of drugs on serum glucose levels in diabetic rat.

Table 5

Effect of drugs on serum glucose levels in diabetic rats [a, b]

Group	Mean + SEM glucose levels (mg/dl)					
	0 hr	1 hr	2 hr	4 hr	6 hr	8 hr
Diabetic control (alloxan 80mg/kg)	364.7± 6.766	358.7 ± 7.688	354 ± 6.245	352.0 ± 4.41	347.1± 3.606	346.7 ± 4.41
Vehicle (1% cmc solution,1ml/rat)	362 ± 5.13	358.7 ± 4.485	356.3 ± 5.667	352.7 ± 6.36	350 ± 7.55	348.3 ± 4.41
Standard (glibenclamide,10 mg/kg)	376 ± 5.859	195.3 ± 2.906	169 ± 2.646	122.3 ± 2.404	192.7 ± 2.33	233.3 ± 4.055
Curcumin (100mg/kg)	347.3 ± 4.485	278 ± 3.606	248.3 ± 4.333	184.7 ± 4.256	236.7 ± 3.528	281.7 ± 3.844
Compound I(100mg/kg)	386.7 ± 1.202	307.7 ± 2.186	258.7 ± 2.33	198.3 ± 2.028	235 ± 2.887	299 ± 8.185
Compound II (100mg/kg)	361.7 ±	229.3 ±	221.3 ±	165.3 ±	147.3 ±	209.7 ±

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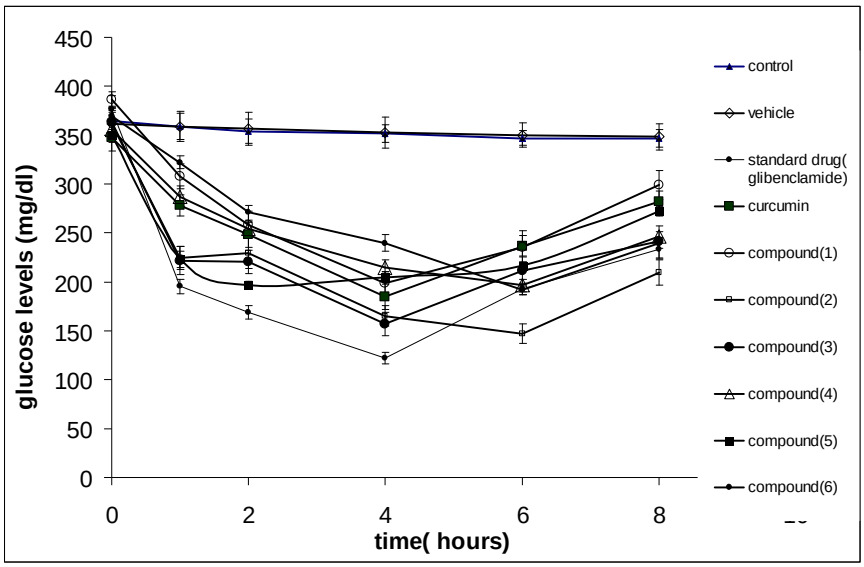
	11.61	6.009	8.090	5.044	5.044	6.33
Compound III (100mg/kg)	363.7 ± 12.14	222 ± 7.234	220.7 ± 6.064	157 ± 5.859	211.3 ± 7.055	241 ± 8.327
Compound IV (100mg/kg)	355.3 ± 5.783	287.3 ± 8.950	254.3 ± 4.631	214.7 ± 5.044	196.3 ± 4.095	246.7 ± 2.963
Compound V (100mg/kg)	349.3 ± 3.383	223.3 ± 4.177	196.3 ± 2.028	205 ± 2.883	216.7 ± 1.764	272 ± 2.517
Compound VI (100mg/kg)	369.3 ± 8.09	322.36 ± 6.74	270.7 ± 7.05	239.7 ± 8.373	191.3 ± 4.667	239.7 ± 5.364

a: all values indicated Mean ±Standard Error Mean(S.E.M) ; b: all groups showed significant decrease in the glucose levels compared to 0 hour level of respective groups; p<0.0001

Figure 2

Effect of drugs on serum glucose levels in diabetic rat



Curcumin, compounds I, and compound V produced maximum activity within 4 hours only and reduced initial serum glucose levels up to 45 %, 48 %, 56% and 41 % respectively. The onset of action of all compounds was observed after 1 hour.

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CONCLUSION

It can be concluded that all the synthesized curcumin structural analogues possessed antidiabetic activity comparable to curcumin in the alloxan induced rat diabetic model. Among the six compounds synthesized, compound II and compound III showed highly significant activity than curcumin and are comparable to standard drug glibenclamide.

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