Curcumin: A Phytoconstituent of Choice

Deepak Phogat, Rajeev K Singla

Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India

Address for Correspondence:

Rajeev K Singla

Assistant Professor

Department of Pharmaceutical Chemistry

School of Pharmaceutical Sciences

Jaipur National University

Jagatpura – Jaipur

Rajasthan-302025

India

Email id: rajeevsingla26@gmail.com

Mobile no. +91-8233306074

Keywords: Curcumin, *Curcuma longa*, Biological Activity, Phytoconstituents, Semisynthetic Derivatives.

Summary

Curcumin, a potential phytoconstituent from the roots & rhizomes of *curcuma longa*, found to be highly medicinally active agent possessing a wide array of activities such as Anti inflammatory , antioxidant , antiprotozoal, nematocidal, antivenom, anti-HIV, anti-tumor, hypolipidemic, hepatoprotective etc. Literature also reveals that derivatives of curcumin possesses Anti tumor, antimalarial, anti angiogenesis, anti HIV, antioxidant, anti inflammatory, antimicrobial and antifungal activity. Current article covers the possible compilation of the relevant information related to the medicinal and therapeutic evaluation of curcumin and its derivatives.

Introduction

Curcumin is the principal curcuminoid of the popular Indian spice turmeric, which is a member of the ginger family (Zingiberaceae). The other two curcuminoids are desmethoxycurcumin and bis-desmethoxycurcumin. The curcuminoids are natural phenols and are responsible for the yellow color of turmeric. Curcumin can exist in at least two tautomeric forms, keto and enol. The enol form is more energetically stable in the solid phase and in solution.[1]

Curcumin can be used for boron quantification in the curcumin method. It reacts with boric acid forming a red colored compound, known as rosocyanine.

Curcumin is brightly yellow colored and may be used as a food coloring. As a food additive, its E number is E100.[2]

Chemistry

Curcumin incorporates several functional groups. The aromatic ring systems, which are polyphenols are connected by two α,β-unsaturated carbonyl groups. The diketones form stable enols or are easily deprotonated and form enolates, while the α,β-unsaturated carbonyl is a good Michael acceptor and undergoes nucleophilic addition. The structure was first identified in 1910 by J. Miłobędzka, Stanisław Kostanecki and Wiktor Lampe.[3]

Curcumin is the principle Curcuminoid of the popular Indian spice turmeric, which is a member of the ginger family (Zingiberaceae). The other two curcuminoids are desmethoxycurcumin and bis- desmethoxycurcumin. The curcuminoids are polyphenols and are responsible for the yellow color of turmeric. Curcumin can exist in at least two tautomeric forms, Keto and Enol. The Enol form is more energetically stable in the solid phase and in solution.[4]

The other two derivatives of *Curcumin (Curcuminoids)* are : P-hydroxyl cinnamoyl feruloyl methane(Curcuminoid- I); p,p-[dihydroxy dicinnamoyl methane(Curcuminoid- 2) and their chemical structures are as below , in order of their composition in turmeric.

CURCUMINOID -1

CURCUMINOID 2
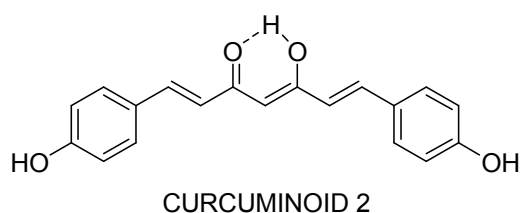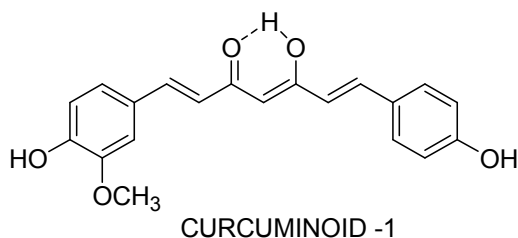
Curcumin is used as a reagent for boron in EPA Method 212.3.[5]

Activities of Curcuma longa

Anti-inflammatory activity [6-8]- Mukophadhyay et al. (1982) demonstrated the activity of curcumin and other semi-synthetic analogues (sodium curcuminate, diacetyl curcumin, triethyl curcumin and tetrahydro curcumin) in carrageenin-induced rat paw edema and cotton pellet granuloma models of inflammation in rats. In these experiments the authors used ferulic acid and phenylbutazone (reference drug). Curcumin and its analogues showed similar action in carrageenin-induced paw edema in rats;

Pharmacological actions of curcumin as an anti-inflammatory agent have been examined by Srimal and Dhawan (1973). In this work, the authors reported that the compound was effective in acute as well as chronic models of inflammation. The potency of this drug is approximately equal to phenylbutazone in the carrageenin-induced edema test, but it is only half as active in the chronic experiments. It was observed that curcumin was less toxic than the reference drug (no mortality up to a dose of 2 g kg-1). Huang et al. (1992) examined the inhibitory effects of curcumin on the proliferation of blood mononuclear cells and vascular smooth muscle cells. In blood mononuclear cells, curcumin was capable to impair the response of cells to mitogen, PHA and the response to alloantigen, MLR. The investigators suggested that curcumin could be use clinically in transplant atherosclerosis. The cinnamic acid derivatives were less active than curcumin. Ammon et al. (1992) demonstrated curcumin as an inhibitor of leucotriene formation in rat peritoneal polymorphonuclear neutrophils (PMNL), with an EC50 of 27 x 10-7 M, in contrast, the hydrocortisone did not show any effect.

Antioxidant activity [9-12]- Unnikrishnan and Rao (1995) studied the antioxidative properties of curcumin and its three derivatives (demethoxy curcumin, bisdemethoxy curcumin and diacethyl curcumin). The authors demonstrated that these substances provide a protection of hemoglobin from oxidation at a concentration as low as 0.08 mM, except the diacethyl curcumin which has little effect in the inhibition of nitrite induced oxidation of hemoglobin.

The effect of curcumin on lipid peroxidation has also been studied in various models by several authors. Curcumin is a good antioxidant and inhibits lipid peroxidation in rat liver microsomes, erythrocyte membranes and brain homogenates (Pulla Reddy & Lokesh 1994). The lipid peroxidation has a main role in the inflammation, in heart diseases, and in cancer.

Turmeric can lower lipid peroxidation by maintaining the activities of antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase at higher levels. These enzymes play an important role in the regulation of lipid peroxidation (Pulla Reddy & Lokesh 1992). Pulla Reddy and Lokesh (1992) observed that curcumin is capable of scavenging oxygen free radicals such as superoxide anions and hydroxyl radicals, which are important to the initiation of lipid peroxidation. Another article about curcuminoids as potent inhibitors of lipid peroxidation was described by Sreejayan Rao (1994), in which the authors showed that three curcuminoids were inhibitors of lipid peroxidation in rat brain homogenates and rat liver microsomes. All of these compounds were more active than a -Tocopherol (drug reference) and curcumin showed the better results. In the case of curcumin, the methoxy group seems to play a major role. The phenolic and the methoxy group on the phenyl ring and the 1,3 _ diketone system seems to be important structural features that can contribute to these effects. The diketone system is a potent ligand for metals such as iron, used in these experiments. Another fact proposed in the literature

is that the antioxidant activity increases when the phenolic group with a methoxy is at the ortho position. The mechanism of action of curcumin is still unknown.

Anti-protozoal activity [13,14]- The first work to relate the activity of curcumin and some semi-synthetic derivatives in the literature against tripanosomatids was studied in promastigotes (extracellular) and amastigotes (intracellular) forms of Leishmania amazonensis. The authors showed that curcumin (a phenolic curcuminoid) in experiments in vitro has an excellent activity (LD50 = 24 µM or 9 mg/ml) and the semi-synthetic derivative, methylcurcumin (a non-phenolic curcuminoid), has the best action with a LD50 < 5 µg/ml and LD90 = 35 µM against promastigotes forms. This derivative was tested in vivo in mice and showed a good activity with 65.5% of inhibition of the lesion size of the footpad of the animals, when compared with the group inoculated with the parasites alone (Araújo et al. 1998, 1999). Another interesting point mentioned by the authors is that they did not observe any inflammatory reaction in the area where the drugs were injected, perhaps because curcuminoids are potent inhibitors of inflammation. Rasmussen et al. (2000) reported the efficacy of an ethanolic extract from C. longa against Plasmodium falciparum and L. major, which was able to inhibit the in vitro growth of these parasites.

Nematocidal activity [15-16]- Curcuma oil was studied on Paramecium caudatum in different concentrations, varying from 1 in 2,000 to 1 in 5,000. The ciliates became sluggish and ultimately died (Chopra et al. 1941). Kiuchi et al. (1993) demonstrated the activity of fractions (methanolic and chloroformic) of turmeric against Toxocara canis. In this work they isolated a new curcuminoid, the cyclocurcumin. All the substances did not show activity when applied independently, but the activity was observed when they were mixed, suggesting a synergistic action between them.

Antivenom activity [17]- A potent antivenom was tested against snakebite. The fraction consisting of ar-turmerone, isolated from C. longa L., neutralized both the hemorrhagic activity and lethal effect of venom in mice. In this study ar-turmerone was capable of abolishing the hemorrhagic activity of Bothrops venom and about 70% of the lethal effect of Crotalus venom. Ar-turmerone can act as an enzymatic inhibitor in the case of venom enzymes, with proteolytic and hemorrhagic activities (Ferreira et al. 1992).

Anti-HIV [18,19]- Mazumber et al. (1995) demonstrated that curcumin has an antiviral activity, being a HIV-1 integrase inhibitor (IC50 = 40 µM) and suggested that curcumin analogs may be developed as anti-Aids drugs. Data showed that curcumin inhibited the replication of HIV-1 integrase protein. Eigner and Scholz (1999) reported that curcumin was claimed for anti-HIV-1 and HIV-2 activities in a recent patent application.

Anti-tumor activity [20,21]- Huang et al. (1988), studying the effect of curcumin, chlorogenic acid, caffeic acid and ferulic acid on tumor promotion in mouse skin by 12-O-tetradecanoyl-13-acetate (TPA), observed that all these compounds inhibit the epidermal ornithine decarboxilase (ODC) and epidermal DNA synthesis, being curcumin the most efficient. In another work (1991), the results suggested that curcumin was a potent inhibitor of TPA- and arachidonic acid-induced inflammation and of lipoxygenase and cyclooxygenase activities in mouse epidermis. The IC50 for curcumin-dependent inhibition of these enzyme activities was 5-10 µM. In this study the results indicated that curcumin inhibited the epidermal metabolism of arachidonic acid via the lipoxygenase and cyclooxygenase pathways.

Furthermore, Ozaki et al. (2000), examining the action of curcumin on rabbit osteoclast apoptosis, demonstrated that curcumin drastically inhibits bone resorption in parallel with its stimulation of apoptosis in the cells. Since cancer and bone inflammation are diseases that increase bone resorption, the authors suggest that curcumin may be useful in the therapy of these pathogenies.

Other activities [22-24] Curcumin and its sodium salt have been showing a strong anti-inflammatory activity in carragenin and caoline-induced edema. Turmeric powder protects the gastric mucosa against irritants. Curcumin can decrease high cholesterol levels like statine and have antimutagenic activity (Scartezzini & Speroni 2000). Chuang et al. (2000) showed that curcumin at concentrations of 200 mg/kg or 600 mg/kg could effectively inhibit diethylnitrosamine-induced liver inflammation in rats. Other interesting action of this substance was demonstrated by Park et al. (2000), when acute hepatotoxicity was induced by intraperitoneal injection of carbon tetrachloride in rats. After these animals had been treated with curcumin and the results showed that the liver injury was inhibited.

Derivatization and pharmacological activities of curcumin

Anti cancer agent[25]

Cyclic diarylheptanoids 13-oxomyricanol **(1a)** and myricanone **(1b)** were studied by **Junko Ishida et al.** (2002). The structure was assigned on the basis of ^{1}H NMR, Mass spectroscopy as well as elemental analysis. The compounds show antitumor activity.

These two compounds **(1a)** and **(2b)** exhibited potent tumor effect on 12-O-tetradecanoylphorbol-13-acetate (TPA) - induced mouse skin carcinogenesis. The compound **(1b)** inhibited Papillioma formation initiated by peroxynitrite. The compound **(1b)** was the most potent analogues against several cell lines, including bone cancer and breast cancer with ED_{50} value of 0.97 and < 0.63 µg/ml.


1 a

1b
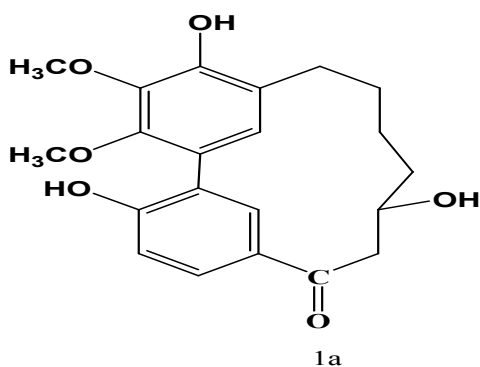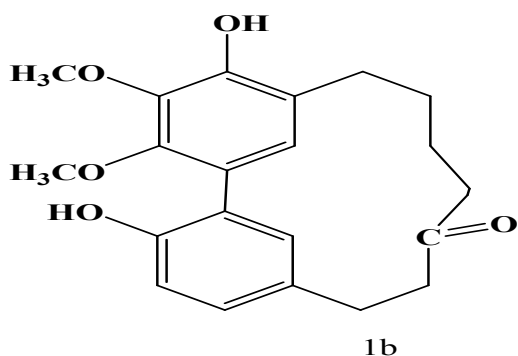
2, 6 Bis (2-Hydroxybenzylidene) cyclohexanone (**1c**), 3, 5 Bis (2-Hydroxybenzylidene tetrahydro-4 H Pyran-4 one) (**1d**) and 3, 5 Bis (2-Fluorobenzylidene) piperidin-4-one (**1e**) were studied by Brain K. Adams et al. (2004). The structure was characterized by ^{1}H NMR, ^{13}CNMR, Mass spectroscopy as well as elemental analysis.

These compounds show the anticancer activity. These compounds inhibit tumor cell growth with a higher potency then the other chemotherapeutics drug (cisplatin). The compound (**1e**) may potentially be an effective chemotherapeutic agent and shows GI_{50} value 0.7µM.

(1c)

(1d)
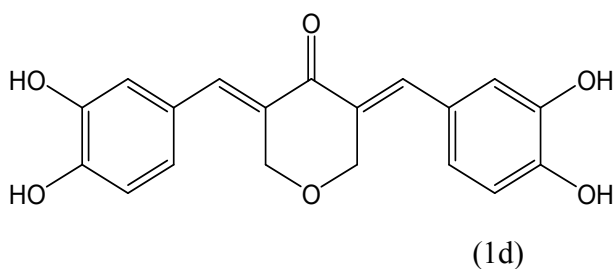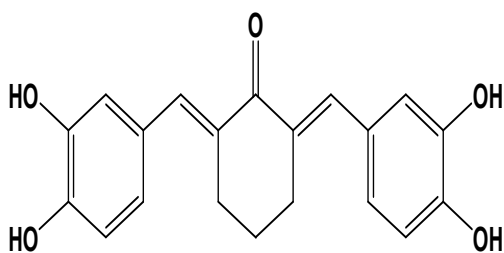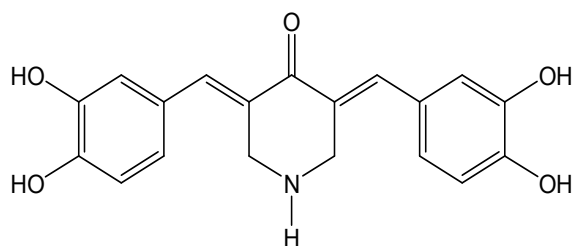
(1e)

[5- Hydroxy 1, 7 bis (3, 4 dimethoxypheny) 1, 4, 6 heptatriene-3-one)] **(1f)**, [5- Hydroxy- 1, 7 bis (3 methoxy-4 methoxy carbonylmethoxy) Phenyl]. [1, 4, 6 heptatriene-3-one] **(1g)**, [7(4 Hydroxy-3-Methoxyphenyl)-4-(3-(4 hydroxy-3 Methoxyphenyl) acryloyl)-5-oxahepta 4,6 dienolic acid ethyl ester] **(1h)** & [bis(3,4 dimethoxyphenyl) 1,3 propanedine] **(1i)** were studied by Hironori ontsu et al. (2002). The structure was characterized by NMR & Mass Spectroscopy, compounds show Anticancer Activity and potent ant androgenic activites. The compound **(1f)** showed the highest antagonist activities and showing a 45% reduction in dihydrotestosterone (DHT) – induced androgenic receptor activity and indicating that the compound **(1f)** is an effective antagonist for androgenic receptor.
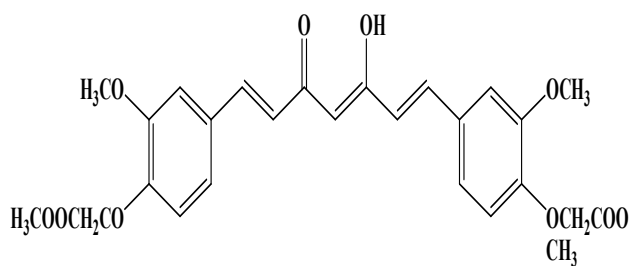
(1f)
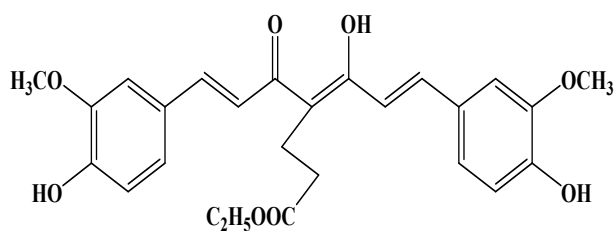
(1g)
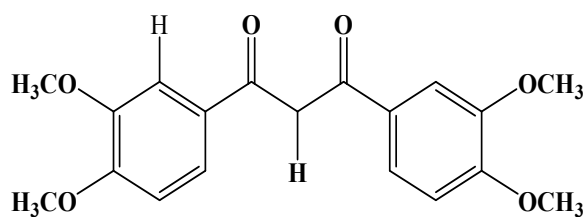
(1h)

Antimalarial agent[26]

Curcumin pyrazole (**2a**), N (3-Nitrophenyl pyrazole) Curcumin (**2b**) & 4[4-Hydroxy- 3 Methoxybenzylidene] Curcumin (**2c**) were study by **Satyendra Mishra et al.** (2008). These compounds were characterized by UV, ^{1}H NMR, and Mass spectroscopy.

These compounds show the anti malarial activity. These compound inhibits chloroquine-sensitive (CQ-S) and chloroquine –resistant (CQ-R) *Plasmodium falciparum* growth in culture with an IC_{50} of ~ 3.25µM and IC_{50} 4.21µM, respectively. The compound **(2a), (2b)** and **(2c)** were inhibitory for CQ-S *P.falciparum* at IC_{50} for 0.48, 0.87, 0.92µM and CQ-R *P.falciparum* at IC_{50} of 0.45µM, 0.89, 0.75µM respectively. The pyrazole analogue of compound **(2a)** exhibited sevenfold higher antimalarial potency against CQ-S and nine fold higher antimalarial potency against CQ-R.
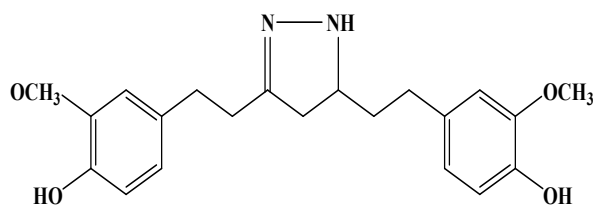
(2a)
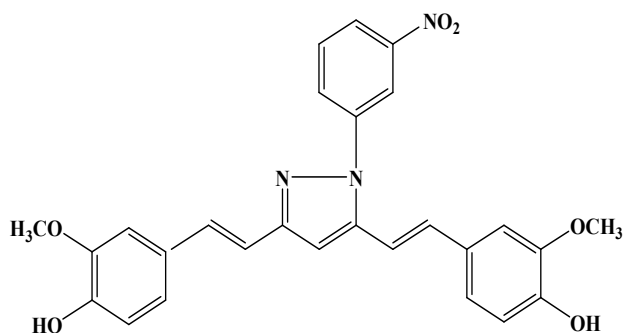
(2b) Fig 2.10
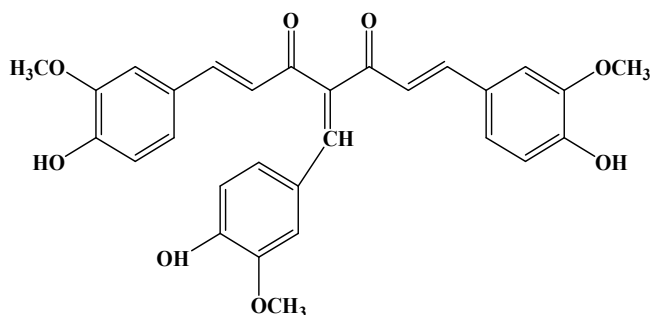
(2c)

Anti angiogenesis agent [27]

1,5 Bis (2-Hydroxyphenylpenta-1,4 dien 3-one) **(3a)**, 3, 5 Bis (2-Fluorobenzylidene) piperidin-4-one **(3b)**, 3,5 Bis (2-Hydroxybenzylidene) tetrahydro- 4- H Pyran-4-One **(3c)** were studied by **Brain K. Adams et al.** (2004). These compounds were characterized by ^{1}H NMR & ^{13}C NMR spectroscopy as well as elemental analysis.
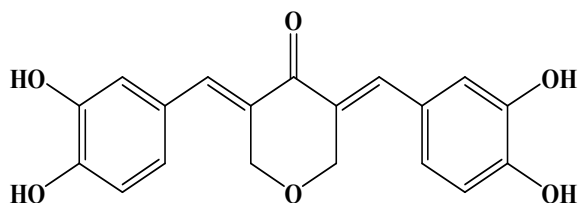
These compounds show antiangiogenesis (inhibition of vascular endothelial cell proliferation invitro and capillary tube formation and growth in vivo). The compound **(3b)** is more potent as and the anti-angiogenic drug TNP-470 and its IC_{50} value 1.5µM.
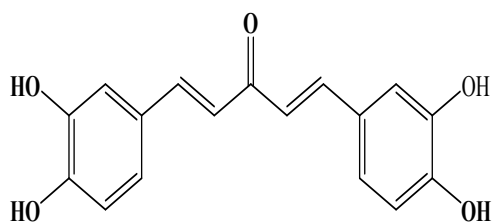
(3a)
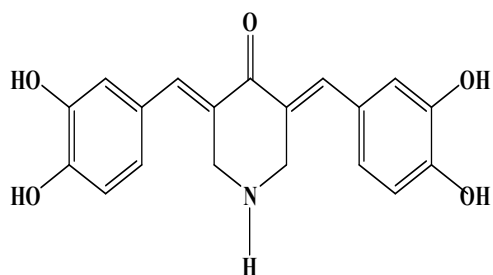
(3b)

(3c)

Hydrozinocurcumin (**3d**), a novel synthetic Curcumin derivative was study by Joong Sup Shim et al. (2002). This compound was characterized by ^1H NMR, ^{13}C NMR spectroscopy. This compound shows antiangiogenesis activity (inhibition of endothelial cell proliferation). The compound (**3d**) potently inhibited the proliferation of bovine aortic endothelial cells at a nanomolar concentration (IC$_{50}$ =520nM) without cytotoxicity.
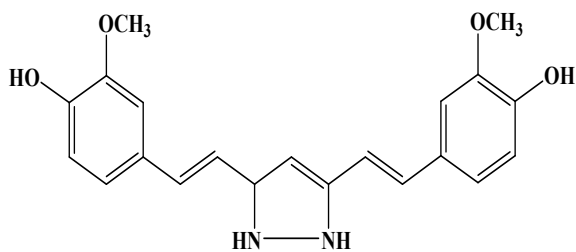

(3d)

Aromatic Enone (**3e**) **&** Dienone (**3f**) analogues of Curcumin were study by Thomas Philip Robinson et al. (2003). The structure of compound is characterized by ^1H NMR & Mass Spectroscopy.

These compounds show the antiangiogenesis (neurovascularization). The aromatic enone and aromatic dienone of analogues of curcumin is excellent antiangiogenic compound. The compound (**3e'**) and (**3e''**) shows 98.2% and 92.8% inhibition of in vitro endothelial cell. Its indicate the compound (**3e'**) is more potent then (**3e''**). The compound (**3f'**) and (**3f''**) shows 94.4% and 87.1% inhibition of in vitro endothelial cell. Its indicate the compound (**3f'**) is more potent then (**3f''**).
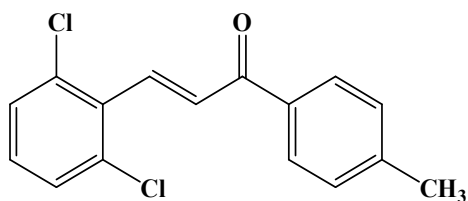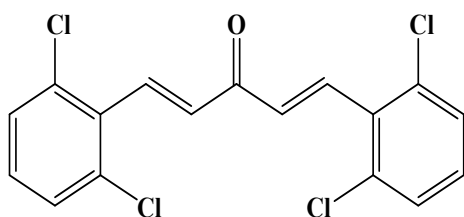

(3e')
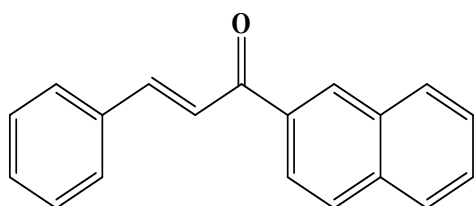
(3e")
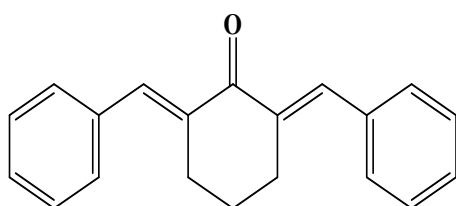
(3f')

(3f")

Anti HIV agent [28]

Dibenzoyl Curcumin (**4a**), Isoxazolcurcumin (**4b**), bi fluoroboron complex of Curcumin (**4c**) were studied by **Zhihu Sui et al.** (1993). The structure was characterized by ^{1}H NMR, ^{13}C NMR Spectra, Mass Spectra as well as elemental analysis.

These compound shows the Anti HIV agent [inhibitor of HIV-1(IC_{50} = 100µM) & HIV-2 (IC_{50} = 250µM) proteases]. These compound (**4b**) is more potent anti HIV activities and shows the HIV-1 (IC_{50} > 100µM) & HIV-2 (IC_{50} = 300µM).

(4a)

(4b)

(4c)
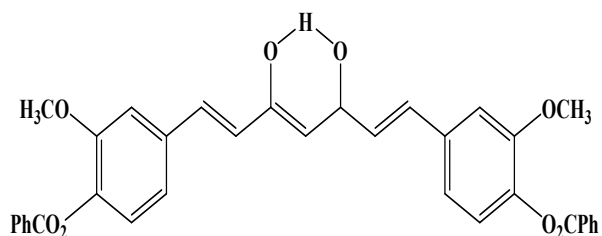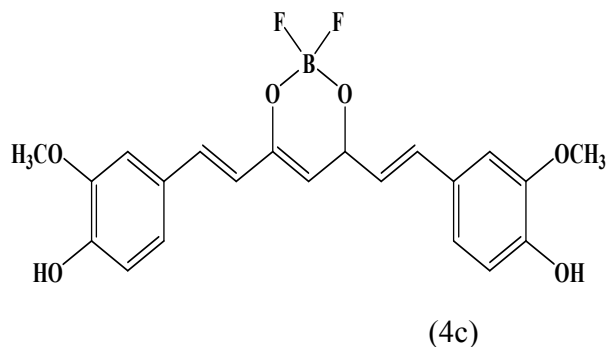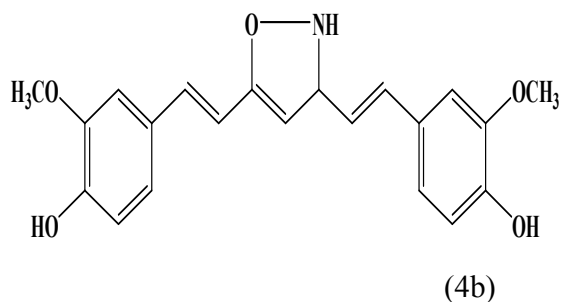
Antioxidant agent[29]

1, 7 Bis (4 Hydroxy 3- methoxyphenyl) - heptane-3, 5 dione (**5a**), 1, 7 Diphenylheptane-3, 5 dione (**5b**) were studied by **Waylon M. Weber et al.** (2005). The structure was assigned on the basis of NMR Spectroscopy. These compound shows antioxidant activity.

The antioxidant activities were determined by Total redical-trapping antioxidant parameter assay (TRAP Assay) & Ferric reducing antioxidant assay (FRAP Assay). The result of the TRAP assay of antioxidant activity is shows the compound (**5b**) more potent. It is not necessary to retain enone or dienone structure of curcumin in order to retain activity. The result of FRAP assay of antioxidant activity is shows the compound (**5a**) is more potent.


(5a)
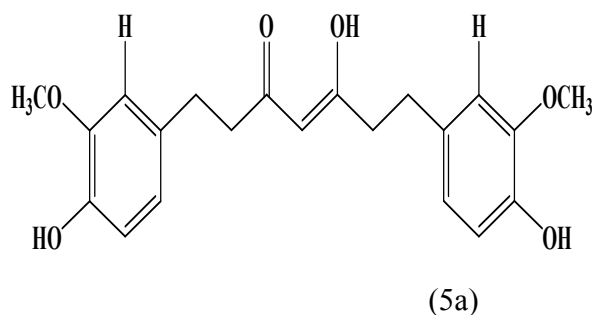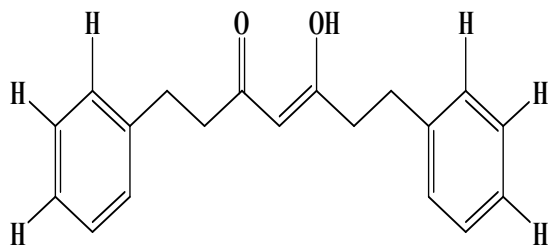
(5b)

2, 6 bis (4 Hydroxybenzylidene) Cyclohexanone (**5c**), 2, 5 bis (4 Hydroxybenzylidene) cyclopentanone (**5d**) & 1, 5 diphenyl 1, 4 pentadiene-3 one (**5e**) were studied by S S Sandjiman et al. (1997). The structures were assigned on the basis of ^{1}H NMR, Mass Spectroscopy.
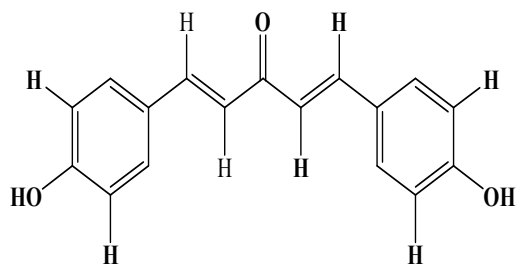
The compounds show the antioxidant activity. These inhibit lipid peroxidation. The antioxidant activity of the compound **(5c), (5d)** and **(5e)** were established in a lipid peroxidation test. The compound shows the 50% inhibition at 4.0μM.
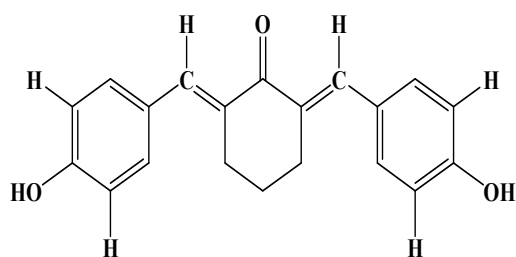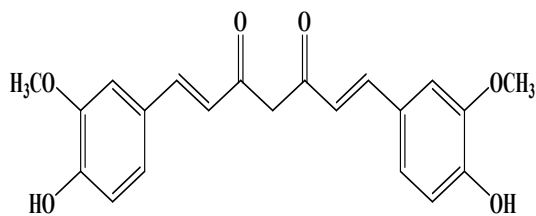

(5c)
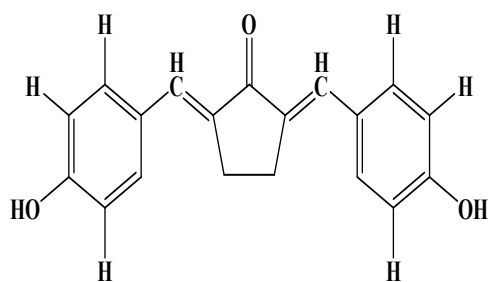
(5d)

(5e)

Anti inflammatory agent[30]

Desmethoxycurcumin (**6a**), bis methoxycurcumin (**6b**) & Tetrahydro Curcumin (**6c**) were studied by **A N Nurfia et al.** (1997). The structure was characterized by NMR & Mass Spectroscopy. These compounds show anti-inflammatory activity.

(6a)
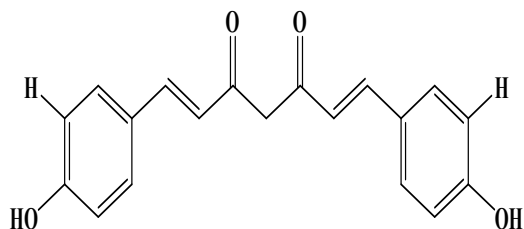
(6b)
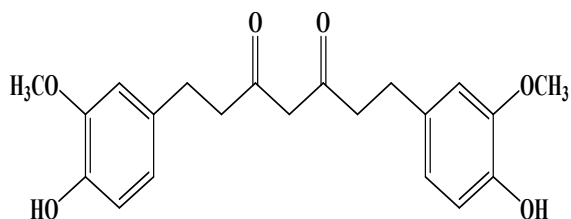
(6c)

Antimicrobial agent & Antifungal agent[31]

4, 4'-(di-o-glutamoyl) Curcumin (**7a**), 4, 4' (di-o-valinoyl) Curcumin (**7b**) & 4, 4'-(di-o-glycinoyl) Curcumin (**7c**) were studied by **Shiv K. Dubey et al.** (2008). The compounds were characterized by ^{1}H NMR & Mass Spectroscopy.

These compounds show antimicrobial activity & antifungal activity. The diester of curcumin are relativily are more active than curcumin itself due to there increase solubility, slow metabolism and better cellular uptake. The monoesters of curcumin have been better antimicrobial activity than their corresponding diester, emphasizing the role of free phenolic group. The conjugate of curcumin with dimethynated piperic acid in which methylenedioxy ring was opened also shows enhanced activity than the corresponding piperic acid conjugate, emphasizing the role of the free phenolics in the transport or in the binding processes.
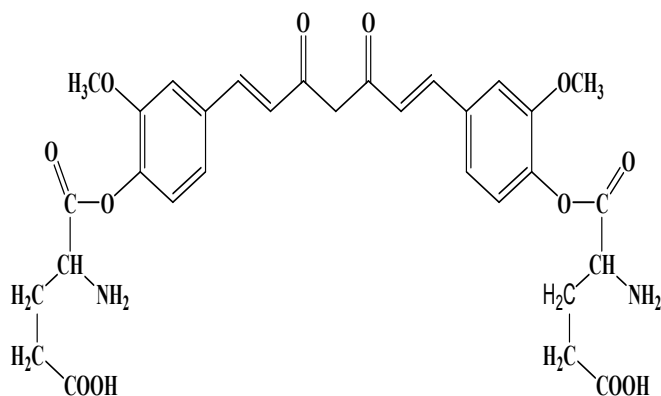
(7a)
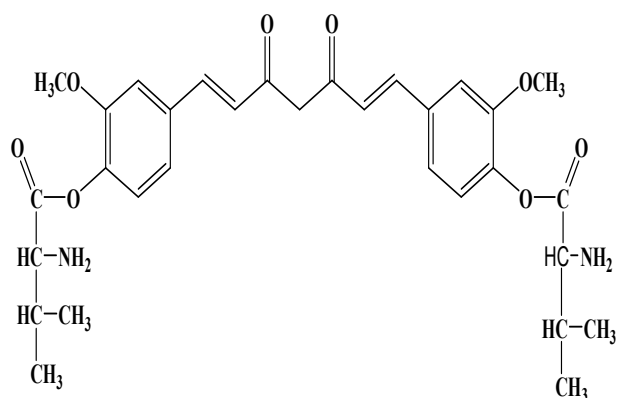
(7b)
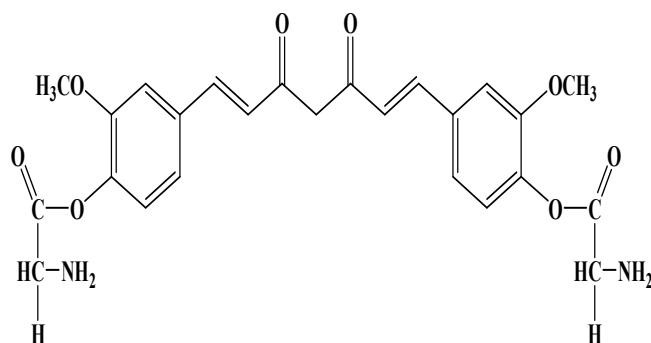
(7c)

References:-

1. Kolev, Tsonko M.; et al. (2005). "DFT and Experimental Studies of the Structure and Vibrational Spectra of Curcumin". International Journal of Quantum Chemistry (Wiley Periodicals) 102 (6): 1069–79. doi:10.1002/qua.20469.

2. Food Standards Australia New Zealand. "Food Additives- Numerical List". Retrieved 2 December 2009.

3. J. Miłobędzka, St. v. Kostanecki, V. Lampe (1910). "Zur Kenntnis des Curcumins". Berichte der deutschen chemischen Gesellschaft 43 (2): 2163–2170. doi:10.1002/cber.191004302168.

4. Kolev, Tsonko M.; et al. (2005). "DFT and Experimental Studies of the Structure and Vibrational Spectra of Curcumin". *International Journal of Quantum Chemistry* (Wiley Periodicals) **102** (6): 1069–79. doi:10.1002/qua.20469.

5. Methods for the Chemical Analysis of Water and Wastes (MCAWW) (EPA/600/4-79/020)

6. Mukophadhyay A, Basu N, Ghatak N, Gujral PK 1982. Anti-inflammatory and irritant activities of curcumin analogues in rats. Agents and Actions 12: 508-515.

7. Huang HC, Jan TR, Yeh SF 1992. Inhibitory effect of curcumin, an anti-inflammatory agent, on vascular smooth muscle cell proliferation. Eur J Pharmacol 221: 381-384.

8. Ammon HPT, Anazodo MI, Safayhi H, Dhawan BN, Srimal RC 1992. Curcumin: a potent inhibitor of Leukotriene B4 formation in rat peritoneal polymorphonuclear neutrophils (PMNL). Planta Med 58: 26.

9. Unnikrishnan MK, Rao MN 1995. Inhibition of nitrite induced oxidation of hemoglobin by curcuminoids. Pharmazie 50: 490-492.

10. Pulla Reddy Ach, Lokesh BR 1994. Effect of dietary turmeric (Curcuma longa) on iron-induced lipid peroxidation in the rat liver. Fd Chem Toxic 32: 279-283.

11. Pulla Reddy Ach, Lokesh BR 1992. Studies on spice principles as antioxidants in the inhibition of lipid peroxidation of rat liver microsomes. Mol Cell Biochem 111: 117-124.

12. Sreejayan Rao MN 1994. Curcuminoids as potent inhibitors of lipid peroxidation. J Pharm Pharmacol 46: 1013-1016.

13. Araújo CAC, Alegrio LV, Castro D, Lima MEF, Leon LL 1998. Leishmania amazonensis: in vivo experiments with diarylheptanoids from Leguminosae and Zingiberaceae plants. Mem Inst Oswaldo Cruz 93 (Suppl. II): 306.

14. Rasmussen HB, Christensen SB, Kvist LP, Karazmi A 2000. A simple and efficient separation of the curcumins, the antiprotozoal constituents of Curcuma longa. Planta Med 66: 396-398.
15. Chopra RN, Gupta JC, Chopra GS 1941. Pharmacological action of the essential oil of Curcuma longa. Indian J Med Res 29: 769-772.
16. Kiuchi F, Goto Y, Sugimoto N, Akao N, Kondo K, Tsuda Y 1993. Nematocidal activity of Turmeric: synergistic action of curcuminoids. Chem Pharm Bul 41: 1640-1643.
17. Ferreira LAF, Henriques OB, Andreoni AAS, Vital GRF, Campos MMC, Habermehl GG, Moraes VLG 1992. Antivenom and biological effects of ar-turmerone isolated from Curcuma longa (Zingiberaceae). Toxicon 30: 1211-1218.
18. Mazumber A, Raghavan K, Weinstein J, Kohn KW, Pommer Y 1995. Inhibition of human immunodeficiency virus type-1 integrase by curcumin. Biochem Pharmacol 49: 1165-1170.
19. Eigner D, Scholz D 1999. Ferula asa-foetida and Curcuma longa in traditional medical treatment and diet in Nepal. J Ethnopharmacol 67: 1-6.
20. Huang MT, Smart RC, Wong CQ, Conney AH 1988. Inhibitory effect of curcumin, chlorogenic acid, caffeic acid and ferulic acid on tumor promotion in mouse skin by 12-O-tetradecanoylphorbol-13-acetate. Cancer Res 48: 5941-5946.
21. Ozaki K, Kawata Y, Amano S, Hanazawa S 2000. Stimulatory effect of curcumin on osteoclast apoptosis. Biochem Pharmacol 59: 1577-1581.
22. Scartezzini P, Speroni E 2000. Review on some plants of Indian traditional medicine with antioxidant activity. J Ethnoparmacol 71: 23-43.
23. Chuang SE, Chen AL, Lin JK, Kuo ML 2000. Inhibition by curcumin of diethylnitrosamine-induced hepatic hyperplasia, inflammation, cellular gene products and cell-cycle-related proteins in rats. Fd Chem Toxicol 38: 991-995.
24. Park EJ, Jeon CH, Ko G, Kim J, Sohn DH 2000. Protective effect of curcumin in rat liver injury induced by carbon tetrachloride. J Pharm Pharmacol 52: 437-440.
25. Ishida J., Ohtsu H. and Nakanishi Y. (2002) 'Antitumor agent: Synthesis and evaluation of curcumin analoghues as cytotoxic agents', *Bioorg. Med. Chem.*, Vol. 10, pp. 3481-3487.
26. Mishra S., Surolia N., and Surolia A., (2008) 'Synthesis and exploration of novel curcumin analoge as antimalarial agent', *Bioorg. Med. Chem.*, Vol. 16, pp. 2894-2902.
27. Adams B.K., Ferstl E.M. and Davis M.C., (2004) 'Synthesis and biological evaluation of novel curcumin analogs as anticancer and antiangiogenesis agents', *Bioorg. Chem.*, Vol. 12, pp. 3871-3883.
28. Sui J., Salto R. and Li J., (1993) 'Inhibition of the HIV-1 and HIV-2 proteases by curcumin and curcumin boron complexes', *Bioorg. Med. Chem.*, Vol. 1, pp. 415-422.
29. Weber M.W., Hunsaker L.A. and Deck L.N., (2005) 'Antioxidant activities of curcumin and related enones', *Bioorg. Med. Chem.*, Vol. 13, pp. 3811-3820.
30. Nurfina A.N., and Timmerman H., (1997) 'Synthesis of some symmetrical curcumin derivative and their antiinflammtory activity', *Eur. J. Med. Chem.*, Vol. 32, pp. 321-327.
31.   Dubey S.K., Sharma A.K. and Narian U., (2008) 'Design, synthesis and characterization of some bioactive conjugates of curcumin with glycine, glutamic acid and study of their antimicrobial and antiproliferative properties', *Eur. J. Med. Chem.*, Vol. 43, pp. 1837-1846.