# Synthesis and structural features of curcumin: A multitargeted component of turmeric

**Abstract**

Curcumin can act as an antioxidant agent by reducing the production of reactive oxygen species (ROS). The important role of turmeric has been investigated as an antispasmodic to reduce menstrual cramping. The multiparametric features of curcumin lead to its various biological importance and are becoming a site of attraction for many researchers. The presence of labile hydrogens, 1,3-diketo groups and their tautomeric forms, α,β-unsaturated linker portions, and aromatic systems are important in various reactions during biological pathways. Curcumin, which has multiple properties, prompted us to investigate the chemistry behind its actions. The literature has provided a limited collection of data that clarify the importance of each substituent for various biological activities. Extensive research is still needed to fully explore and understand the underlying chemistry and therapeutic potential of these medicinally important entities.

**Keywords**: Therapeutic potential, curcumin, reactive oxygen species, medicinal properties

# Introduction

Ayurveda is the most ancient platform that produces turmeric in the form of its medicinal properties. “Turmeric” has been a universal herbal medicine since ancient times, with a broad variety of pharmacological actions. The name turmeric is drawn from the Latin word ‘terra merita’, which means “meritorious earth”, referring to the color of land turmeric that resembles a mineral dye.1-2 It is an inexpensive spice that is still used in the rituals of the Hindu religion and in the food industry as a coloring agent and food preservative. Moreover, it has also been used extensively by Indian brides and young girls for healthy and glowing skin color in the form of natural face masks.1-5 Turmeric milk, along with other herbs, is commonly used to cure the common cold, cough, and fever and to relieve pain during such processes. In the treatment of many different health circumstances, turmeric is a natural wonder that has numerous health benefits. The main benefits of turmeric as a natural antiseptic, antiviral, antibacterial, and anti-inflammatory agent have been discussed.2, 6-8 Narsi, H. *et al.* demonstrated the role of turmeric (mainly curcumin) as an anticarcinogenic agent that inhibits carcinogenesis, mainly at the angiogenesis and tumor promotion stages. Several studies have revealed that it also inhibits cell proliferation and tumor growth in colon and prostate cancer.3, 9-12 Turmeric also affects inflammation by inhibiting the reactive oxygen species (ROS) and NF-kB pathways. It suppresses proinflammatory mediators such as interleukin-1 (IL-1), IL-1β, IL-6, IL-8, IL-17, IL-27, and tumor necrosis factor-α (TNF-α). In addition to this property, it inhibits cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) enzymes.4- 5, 13-14 Furthermore, curcumin can act as an antioxidant agent by reducing the production of reactive oxygen species (ROS). Narsi, H. *et al.* reported the prevention of hemoglobin oxidation.3, 9, 15 The turmeric rhizome, its juice, and dry powder are rich sources of iron, which is useful for the treatment of anemia. D Bhowmik *et al.* reported that turmeric is helpful in treating intestinal problems, especially diarrhea and other digestive disorders. In addition, curcumin is useful for reducing cholesterol levels and inhibiting

oxidation of low-density lipoprotein (LDL).2, 16 Recently, studies have explored the role of curcumin in many other diseases, such as Alzheimer's disease. S.D. Voulgaropoulou and coworkers have worked and provided some evidence for the importance of curcumin in the treatment of Alzheimer's disease by removing amyloid plaque buildup in the brain.2, 9 Research is still in progress to investigate the multiparametric effects of curcumin on many diseases. Another important role of turmeric has been investigated as an antispasmodic to reduce menstrual cramping. Some researchers have provided data indicating that internal pain during the menstrual cycle can be cured with turmeric supplements. Nevertheless, much research has been carried out in the field to explain the chemistry behind such biological actions. Data are still lacking that can explain the hormone imbalance process and its proper function by taking these supplements. 2, 17-18

Curcumin is a yellow and nontoxic component of turmeric, which belongs to the Zingiberaceae family. It is used for cooking spicy food, cosmetics and traditional Ayurveda medicine.19-21 It has many biological properties, such as antibacterial, antifungal, antioxidant, anticancer, anti-inflammatory, anti-Alzheimer, antitumor, antiviral, anti-carcinogenic, anti-HIV, cough, anti-diabetic, blood purifier, and anti-proliferative properties, with certain limitations such as poor absorption, low bioavailability and rapid metabolism.22-24 Turmeric also has other derivatives of curcumin, which are demethoxy curcumin and bisdemethoxy curcumin. These analogs also have biological properties. Curcumin has three important constituents: (i) a 1,3-dicarbonyl as a linker, (ii) two aromatic rings connected on both sides with methoxy and hydroxyl groups, and (iii) an active methylene group, which participates in keto-enol tautomerism.25-28

* 1. Composition of the Turmeric Rhizome

**Table 1a.** The composition of Turmeric rhizome1, 9-10, 15, 17, 29-30

|  |  |  |
| --- | --- | --- |
| Component | Composition | Percentage (%) |
| Turmeric | Carbohydrates Fats Proteins Fiber Minerals Moisture | 60-705-106-82-73-77-8 |
| Curcuminoids | Curcumin ICurcumin II Curcumin III | 1-980173 |
| Essential Oils | Sesquiterpenes Zingebereneα-phellandrene d-sabinene CineolBorneol | 532010.610.5 |

Note: - Curcumin I: Curcumin, Curcumin II: Demethoxycurcumin (DMC), Curcumin III: Bis-demethoxycurcumin (BDMC)

Table 1.a shows that turmeric contains greater amounts of curcumin I ((1E,6E)-1,7- bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) than other curcuminoids, i.e., curcumin II (DMC) and curcumin III (BDMC). It is an initially isolated yellow spice that also exists in keto-enol form (Figure 1.a). The molecular formula of curcumin is C21H20O6, and its molecular weight is 368.39 g/mol.1, 3, 10, 15, 29-30

## Characteristic features of curcumin

Curcumin exists in two tautomeric forms (1 and 2). The existence of these tautomers depends upon various factors, such as the stability of the tautomer, solvent, and polarity. In nonpolar and moderately polar solvents, the enol form is generally more preferred than the keto form. In the crystalline state, curcumin mainly exists in a cis-enol configuration, which is stabilized by resonance-assisted hydrogen bonding. On the other hand, in the solution phase, it exists in a trans-enolic form where the configuration of the Pi-electron clouds is dispersed completely throughout the whole molecule (Figure 1.a). The dipole moment of curcumin in the ground state is 10.77 D, which is calculated computationally. Curcumin is hydrophobic in nature, with a LogP value of

~ 3.0. It is insoluble in water but has shown solubility in solvents such as dimethyl sulfoxide (DMSO), methanol, ethanol, and acetone. Furthermore, strong absorption bands of curcumin were observed in the UV spectra. One band exists in the visible region in the range of 410–430 nm, and a second band exists at 265 nm. The molar extinction coefficient is 55000dm3mol--

1 cm-1 at 425 nm in methanol.1, 15, 31-32

**Figure 1.a.** Structures of curcuminoids

## Chemical Reactivity of Curcumin

The multiparametric features of curcumin lead to the various biological importance of curcumin, which has attracted the attention of many researchers. The presence of labile hydrogens, 1,3-diketo groups and their tautomeric forms, α,β-unsaturated linker portions, and aromatic systems are important in various reactions during biological pathways. Therefore, before investigating the chemistry behind the action of curcumin on various biological properties, it is important to understand the reactivity of curcumin.31, 33 Some possible reactions have been discussed as follows:

### Degradation

The chemical degradation of curcumin is pH dependent. The degradation of curcumin is increased in alkaline media (pH>7), and curcumin is degraded into trans-6-(4’- hydroxy-3’-methoxyphenyl)-2,4- dioxo-5-hexanal, ferulic acid, feruloyl-methane, and vanillin (Figure 1.b).3, 31, 33-37

**Figure 1.b.** Chemical structures of curcumin degradation: trans-6-(4’- hydroxy-3’- methoxyphenyl)-2,4-dioxo-5-hexanal (3), ferulic acid (4), feruloyl-methane (5), and vanillin (6)

The linker part, i.e., the α,β-unsaturated 1,3-dicarbonyl moiety, is mainly responsible for the degradation process, as proposed by various research groups. When curcumin is combined with lipids, liposomes, cyclodextrins, etc., its degradation decreases. Oxidative degradation can also be created by light absorption (photodegradation). This process generates singlet oxygen and other reactive oxygen species that are responsible for the photobiological activity of curcumin.2-3, 31, 33

### Reactivity with reactive oxygen species (ROS)

Reactive oxygen species (ROS), which include both free radical oxidants and molecular oxidants, are involved in hydrogen abstraction and electron transfer reactions. The three labile hydrogens, two sites from the phenolic moieties and one from the linker segment of curcumin (enol form), take part in oxidation by electron transfer and hydrogen abstraction (Figure 1.c).1, 3, 9, 31, 35, 38-39

## Figure 1.c. Possible sites of attack of the free radical oxidants of curcumin

### Curcumin–metal ion interactions

***The*** α,β-unsaturated 1,3-dicarbonyl moiety of the linker in curcumin forms strong complexes with various metal ions. Metal bond formation is increased by the replacement of the proton of

the enolic group with a metal ion. Curcumin-metal complexes affect biological actions. Compared with that of curcumin, the antitumor activity of metal-curcumin complexes is enhanced. These compounds also act as antioxidants and pro-oxidants in biological activities. However, the data are still unclear for the activity of metal complexes, which depends upon various factors, such as the nature of the metal, stability, and coordination number, and more chemistry behind such types of compounds is needed in the future.31, 35, 40

**Figure 1.d. Structure of the CUR-metal complex**

# Synthesis of Curcumin

* 1. **Conventional methods:** In this method, the free state of curcumin is not obtained. However, owing to the formation of the boron complex, a brick red color is obtained in acidic media, and a purple color is obtained in basic media. At higher temperatures, the yield is lower than that at room temperature. The optimal temperature range for the synthesis of curcumin is 85–110°C. To improve the yield, an ethyl acetate solvent is used. Tri-isopropyl borate and tri-second butyl borate solvents also increase the yield of curcumin.31, 41-42

**Scheme 1.** Synthesis of Curcumin

* 1. Compared with the conventional method, the microwave-assisted method results in a high yield with better purity. At higher powers during microwave irradiation, the control of the reaction course is not perfect. Owing to the polar nature of the solvent, the pure powder product is soluble in methanol. If curcumin reacts with water, its yield decreases. The cis-enol form of curcumin occurred in the crystal state. Curcumin is insoluble in water but readily soluble in polar solvents such as DMSO, methanol, ethanol, acetonitrile, chloroform, and ethyl acetate. In addition, it is soluble in hydrocarbon solvents such as cyclohexane and hexane. However, in some cases, the yield decreased under microwave irradiation**.**31, 41-42

## Structural activity relationships and multifaceted actions of curcumin and its analogs

Curcumin has various biological activities, such as traditional Ayurveda medicine1 antioxidant, anticancer, anti-inflammatory,4,13,29,35 antibacterial, antifungal,43-44 antiviral,8,45-46 anti-Alzheimer,47-48, antidiabetic, etc.49 However, the present work has focused mainly on anticancer and anti-inflammatory properties. Many research groups have investigated derivatives that act as anticancer and anti-inflammatory agents.

The structural activity relationship of curcumin has been investigated by different researchers. The basic structural framework of curcumin consists of two major components: a symmetrical aromatic system with hydroxyl and methoxy substituents and a linker moiety consisting of an α,β-unsaturated 1,3-dicarbonyl unit. Both of these units play a vital role in various biological activities.11,12,31,50-51

## Structural features of the linker in curcumin

Curcumin exists in two tautomeric forms, i.e., keto and enol (**1** and **2**), which have been shown to have various biological properties.11,12,31,50-51 Furthermore, the enol form of curcumin has attracted some research groups, as it has been shown to be more effective than the keto form in terms of its antioxidant and anticancer properties. On the other hand, the presence of a 1,3-dicarbonyl group (Keto form) generated many complexes with various metals that are beneficial for binding. Its enolic form, which tends to be more stable than the keto structure, is important for metabolism, degradation, and antitumor activity **(Figure 2.a)**.39,52-54

## Structural features of the aromatic moiety of curcumin

The presence of two aromatic moieties in curcumin is responsible for various enzyme activities. The two substitutions, i.e., hydroxyl and methoxy groups, in these aromatic systems are important for their antioxidant, anti-inflammatory, and, to some extent, antitumor activities. The methoxy group on the aromatic ring has anti-inflammatory and antitumor effects, and along with the phenolic moiety, it has exposed antimalarial activity. Moreover, the radical scavenging property of curcumin is due to the presence of two hydroxyl groups (in the keto form). On the other hand, the enolic form of curcumin, which contains three hydroxyl groups, is liable for increased antioxidant activity.3,33,39,52-55

Demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) are also naturally occurring compounds that have demonstrated potency against cancer cell lines *in vitro* and differ from curcumin in terms of position and number of hydroxyl and methoxy substitution patterns.

**Figure 2.a.** Structures of curcumin: keto form (1) and enol form (2)

Other curcumin-like compounds, such as tetrahydrocurcumin (THC), hexahydrocurcumin (HHC), and octahydrocurcumin (OHC), have also shown potential for anticancer activity **(Figure 2.b)**.44, 56-61

The radical scavenging activity of curcumin was similar to that of DMC and BDMC. Compared with curcumin, the enolic form of Dimc has been shown to be more effective in prostate cancer and hepatocarcinoma.62

Various research groups have investigated derivatives of curcumin and synthesized more potent anticancer and anti-inflammatory curcumin-like compounds. To overcome the drawbacks of curcumin, the cyclization of 1,3-dicarbonyl, metal chelation, the introduction of heteroatoms, and the replacement of the active methylene group in the linker section have been practiced.39,54,62 A detailed literature survey was carried out to investigate and analyze the nature of new derivatives of curcumin in comparison to that of curcumin. Broadly, some specific sets of derivatives have been selected from the literature to refine the understanding of their chemical and biological activities.

**Figure 2.b.** Some curcumin-like compounds

## Structural features of new linker-based curcumin derivatives

The literature provides extensive data regarding the various effects of linkers on the biological properties of curcumin-like compounds. In the linker part, when the active methylene group was replaced with the acetoxy group (9) in the enolic form, the anticancer activity was better than that of curcumin toward hepatocarcinoma and colon and prostate cancer. Compounds 10-19, containing various aromatic moieties in the methylene group, have been shown to have antimalarial and anti-inflammatory activities **(Figure 2.c)**39, 62

The insertion of different phenyl groups at the active methylene group in the linker portion (10--13) has been shown to affect various biological activities. A decrease in antimalarial activity was found in a compound in which the para position was occupied by a hydroxyl group (10) compared with curcumin. On the other hand, the phenyl rings of compounds 13--15, which were substituted with two/three hydroxyl groups or amine groups, have shown entirely different properties. It was observed that with an increase in the number of hydrogen bond donors, there was little increase in solubility and a decrease in lipophilicity.

In contrast, the compounds (16--18) with methoxy substituents at the para position of the phenyl ring presented a decrease in solubility and an increase in lipophilicity.39, 62

**Figure 2.c.** Anticancer, anti-inflammatory, and antimalarial curcumin-like compounds

Furthermore, the phenyl ring was substituted with a hydroxyl group at the para position, and the methoxy group at the ortho position was poorly soluble (19). Compounds 13--14 exhibited low gastrointestinal absorption, and compounds 14, 18, and 19 violated Lipinski’s Rule of Five **(Table 2.a)**.39,55 Therefore, it may be concluded that the amine group, the position of the hydroxyl and methoxy groups, and the results of physicochemical and pharmacokinetic studies play crucial roles in the potency of compounds against various diseases.

**Table 2a.** Physicochemical and pharmacokinetic studies

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Compound** | **MW** | **HBA** | **HBD** | **LogP** | **LogS** | **GI** | **DL** |
| 1 | 368.38 | 6 | 2 | 3.37 | -4.45 | High | Yes |
| 2 | 368.38 | 6 | 3 | 3.17 | -3.61 | High | Yes |
| 9 | 426.42 | 8 | 3 | 2.95 | -3.64 | High | Yes |
| 10 | 472.49 | 7 | 3 | 3.55 | -5.69 | High | Yes |
| 11 | 472.49 | 7 | 3 | 3.56 | -5.69 | High | Yes |
| 12 | 472.49 | 7 | 3 | 3.37 | -5.69 | High | Yes |
| 13 | 488.49 | 8 | 4 | 3.44 | -5.56 | Low | Yes |
| 14 | 504.48 | 9 | 5 | 3.63 | -5.42 | Low | No |
| 15 | 471.50 | 6 | 3 | 3.38 | -5.47 | High | Yes |
| 16 | 486.51 | 7 | 2 | 4.11 | -5.91 | High | Yes |
| 17 | 486.51 | 7 | 2 | 3.95 | -5.91 | High | Yes |
| 18 | 516.54 | 8 | 2 | 3.86 | -5.64 | High | No |
| 19 | 502.51 | 8 | 3 | 4.34 | -5.77 | Low | No |

**Note:** Physicochemical parameters calculated via SwissADME software: MW = Molecular weight; TPSA = Topological polar surface area; HBA = Hydrogen bond acceptors; HBD = Hydrogen bond donors; LogP = Lipophilicity; LogS = Water solubility parameter; DL = Drug-likeness; GI = Gastrointestinal absorption; BBB = Blood–brain barrier; P-gp = Poly-glycoprotein substrate

## Structural features of new curcumin derivatives with monocarbonyl linkers

The presence of the α,β-unsaturated 1,3-dicarbonyl linker part of curcumin has shown its importance in different biological properties. The literature revealed several new derivatives whose structures resembled those of curcumin but contained monocarbonyl linker moieties instead of 1,3-dicarbonyl units. Through such replacement, drastic changes in the biological properties were observed. Compared with curcumin derivatives, monocarbonyl derivatives have been shown to be more effective for anticancer and anti-inflammatory activities but to have a reduced effect on metal chelation.

In such monocarbonyl derivatives, the meta- and para-substituted hydroxyl groups on the aromatic ring were less potent than the ortho-substituted compounds were (22-24).54, 63

**Figure 2.d.** Linker-based anti-inflammatory and anticancer curcumin-like derivatives

## Structural features of new curcumin derivatives containing heteroatoms

Furthermore, the five- and six-membered cyclic groups containing heteroatoms in the linker portion have shown enhanced potency toward anticancer activity (28-31). Another set of compounds that consists of heteroatoms in five- and six-membered aromatic moieties has also revealed significant anticancer activities (32- 35). Compounds 31 and 32 have been shown to be potent against triple-negative breast cancer **(Figure 2.e)**.54, 63-64

A critical analysis of the chemical structure and position of heteroatoms in such compounds revealed that the efficacy of the compounds depends upon many parameters. The presence of various heterocyclic moieties at different positions (instead of aromatic moieties in curcumin) has signified their potency toward various biological activities. These heteroatoms are involved in the structural interactions of many target sites. The literature reveals some clarifications regarding the enhancement of the efficiency of such biological activities, which still have to be investigated for their structural interactions.

**Figure 2.e.** Compounds that contain heteroatoms in aromatic moieties

## Structural features of the unsymmetrical curcumin derivatives

The literature also provides data concerning unsymmetrical monocarbonyl curcumin-like derivatives. Compared with symmetrical analogs, compounds 36--39 exhibit more efficient anti-inflammatory activity by inhibiting the lipopolysaccharide (LPS)-induced discharge of tumor necrosis factor (TNF)-α and interleukin-6 (IL-6). Unsymmetrical curcumin-like compounds play an important role in increasing the efficiency of compounds toward biological activities (40-42) **(Figure 2.f)**.63

Curcumin, which has multiple properties, prompted us to investigate the chemistry behind its actions. The literature has provided a limited collection of data that clarify the importance of each substituent for various biological activities. Collectively, the orientations of different substitutions, their numbers, and their positions are some of the important points that are still to be discussed. Even slight variations in their structure can complicate their biological activities. Therefore, to work with such a system, the structural framework of curcumin should be understood, and the design of a new pharmacophore should be imagined.

**Figure 2.f.** Unsymmetrical monocarbonyl curcumin-like derivatives

## Conclusion

The structural diversity and biological significance of these moieties highlight their crucial role in modulating various pharmacological properties. Each functional group contributes significantly to enhancing bioactivity, making them valuable scaffolds in drug discovery. However, extensive research is still needed to fully explore and understand the underlying chemistry and therapeutic potential of these medicinally important entities.

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