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REGULAR ARTICLE

Is curcumin a good scavenger of reactive oxygen species? A computational investigation

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Abstract A computational analysis of chemical structures and biomolecular properties of curcumin, the most important component of turmeric, are carried out by means of state-of-the-art methods of calculations. High-level ab initio calculations (G4) along with reliable methods of density functional theory have been used to study all probable mechanisms of curcumin with reactive oxygen species including hydrogen atom transfer, single electron transfer, radical adduct formation and sequential proton loss electron transfer. The calculations have been carried out in solutions of water and n-octanol in order to mimic the role of blood serum and lipid environment in human bodies. Radical stabilization energies are also studied to explore the radical scavenging ability of curcumin and other related derivatives. With the aim of designing more effective species in terms of improved antioxidant activity and solubility, some curcumin-like molecules with different substituents have been also investigated.

Keywords Curcumin · Radical scavenging activity · Density functional theory · Theoretical organic chemistry · Molecular design

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1 Introduction

In recent years, the field of free radical chemistry attracted great attentions because of its importance in biochemistry, polymer chemistry and so forth. In the biological system, reactive oxygen species (ROS) are free radicals that are derived from oxygen molecule [1]. ROS include superoxide anion ($O_2^{\bullet-}$), perhydroxyl radical ($^{\bullet}OOH$), hydroxyl radical ($^{\bullet}OH$) and singlet oxygen ($^1O_2$) [1]. Oxidative stress (OS) leads to the free radical damage to cellular membrane lipids, DNA and proteins and consequently leads to many diseases such as atherosclerosis, cancer, diabetics, Alzheimer's disease, rheumatoid arthritis and chronic inflammation in humans [2, 3]. Antioxidants play a key role in controlling the level of free radicals. Curcumin, the major component of turmeric, is a non-enzymatic phenolic antioxidant that is ten times stronger than vitamin E in scavenging free radicals [4, 5]. Several experimental and theoretical calculations have been carried out on the structure of curcumin, and the enol isomer is reported to be more energetically stable and dominate form in both gas phase and solution [6–10]. In contrast, a recent study reported that the diketo is more stable than the enol form [11].

Determination of the active site and elucidation of reaction mechanisms are important for investigation of antioxidant activity of curcumin. Several theoretical and experimental studies are carried out on ROS scavenging activity of curcumin. For example, recently, Agnihotri et al. investigated scavenging mechanism of curcumin toward the hydroxyl radical based on theoretical study at different levels of theory in gas phase and in aqueous media. They considered all probable mechanisms such as hydrogen atom transfer (HAT), single electron transfer (SET) and radical adduct formation (RAF) and reported that by HAT mechanism, hydrogen atom of phenolic

hydroxyl was the most efficiently abstracted atom by OH radical [12]. Galano et al. focused on the role of the reacting free radicals on the antioxidant mechanism of curcumin from a theoretical point of view [13]. They have considered different mechanisms for reaction of curcumin with $^{\cdot}OCH_3$ radical including HAT, RAF, SET and sequential proton loss electron transfer (SPLET) in water and benzene solutions and proposed that for reaction of curcumin with 1,1-diphenyl-2-picrylhydrazyl radical (DPPH), SPLET mechanism is favorable, while with $^{\cdot}OCH_3$ and other alkoxyl radicals, the reaction was governed by HAT mechanism [13]. They also suggested that the favorite site for addition of methoxy radical was the central carbon of curcumin chain [13].

Jovanovic et al. also studied antioxidant mechanisms of curcumin by laser flash photolysis and pulse radiolysis and reported that in neutral and acidic aqueous solutions, the keto form of curcumin dominated and was appropriate for HAT mechanism [14]. In contrast, Priyadarsini et al. based on biochemical, physicochemical and density functional theory (DFT) studies reported that although removing hydrogen from both the phenolic OH and the CH_2 group of the diketo structure was very close to one another energetically, the phenolic OH was essential for both antioxidant activity and free radical kinetics [15]. Ak and her worker also determined the antioxidant activity of curcumin in vitro and reported that curcumin can scavenge free radicals such as superoxide anion radical and hydrogen peroxide. Antioxidant activity of curcumin was interpreted as H-atom transfer from the phenolic hydroxyl group [16].

Feng et al. studied curcumin and reported that among phenolic and enolic hydroxyl groups the antioxidant abilities of curcumin was related to H-atom donating from phenolic hydroxyl [17]. Kumuda et al. investigated the possible antioxidant properties of curcumin using electron paramagnetic resonance (EPR) spectroscopic techniques and showed that curcumin was able to eliminate singlet oxygen ($^1O_2$) at very low concentration in aqueous systems [18].

Many experimental and theoretical research provided significant amount of data on antioxidant activity and scavenging free radical ability of curcumin [12–18]; nonetheless, there is still a need for a comprehensive study on the understanding of chemical properties of curcumin and basic mechanisms of its reactions with ROS. In the present work, we investigated ROS scavenging ability of curcumin, considering probable mechanisms such as HAT, SET, RAF and SPLET based on reliable computational methods. In addition, radical stabilization energy (RSE) was calculated as a parameter for comparison between the antioxidant property of curcumin and related species. The effect of substituents on the activity and solubility of curcumin was also examined.

2 Computational details

As recommended by Curtiss and his co-workers, the equilibrium molecular geometries were optimized at the B3LYP level of theory using 6-31G(2df,p) basis set [19]. It is known that the use of B3LYP/6-31G(2df,p) level of theory for geometry optimization leads to an improvement in overall results compared to MP2 theory, which previously was used in the formulation of G3 theory [20]. This recommended level of theory is now used in G4 theory [19]. Vibrational frequencies were computed at the same level of theory as the geometry optimization to provide zero-point energies (ZPEs) and other thermal corrections considering the scale factor of 0.9854 [19].

According to the size of studied molecules and hardware limitations, G4 calculations were not applicable here. Instead, the single-point energy calculations were performed for each optimized geometry using the reliable DFT method of BMK [21] together with basis sets of 6-311+G(3df,2pd) and 6-311+G(d,p). BMK functional which was introduced by Boese and Martin is recommended for both transition states and equilibrium properties [21]. An ONIOM approximation to G4 was employed, in which the core of reaction (designed to include the reaction center and all primary substituents) was studied at G4 and the remaining remote substituent effects were studied at lower level of theory, BMK/6-311+G(3df,2pd). Solvation energies are calculated using solvation model density (SMD) at the M05-2X/6-31G(d) level of theory which has been suggested by Truhlar and his co-workers [22]. Gaussian 09 was used for all ab initio and DFT calculations [23].

3 Results and discussion

3.1 Enol–diketo tautomerism

Chemically, curcumin is a member of polyphenol class of natural products in which two *ortho*-methoxy phenols are linked together through a seven unsaturated carbon chain. It consists of an α,β-unsaturated β-diketone moiety that exhibits keto–enol tautomerism (Fig. 1) [24]. In order to estimate the relative stability of the enol/diketo forms, the electronic energies and Gibbs free energies (at 298 K) have been calculated for the studied forms presented in Fig. 1. For a smaller model, where the remaining group is replaced by H-atom, the thermodynamic quantities have been calculated using both BMK functional and G4 theory, but for the outer layer, BMK functional has been used to calculate the change in thermodynamic functions considering the size of molecules. The results of BMK are in good agreement with G4 theory with deviations less than 2 kJ mol^{-1}. For the sake of brevity, the results are summarized in Table S2

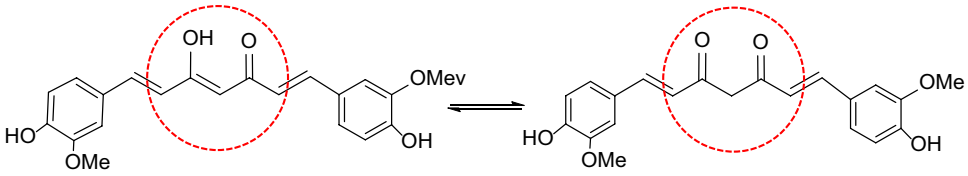

Fig. 1 Enol (*left*) and diketo (*right*) forms of curcumin. The *dotted ring* shows the core which was studied by both BMK and G4 methods

in Supporting Information (SI). The relative populations of [diketo]/ [enol] have been obtained much smaller than unit using Boltzmann's equation [25] based on G4 and BMK. Therefore, the dominant form of curcumin is the enolic form. It is worth noting that for the enol form, there is an intra-hydrogen bonding. This extra hydrogen bonding makes the enol form more stable than the diketo form. Besides, in the enol form, there is a long conjugated π-electron system which gives extra stability to the molecule. This is in agreement with our previous study [26] and reported experimental results [27, 28].

The free radical scavenging capacity of enol form for ROS radicals including $^{\cdot}OH$, $^{\cdot}OCH_3$, $^{\cdot}OOH$ and $O_2^{\cdot-}$ is studied in relation with four known mechanisms: SET, RAF, SPLET and HAT. Since curcumin passes through hydrophobic channels such as lipid bilayers of cells and aqueous regions such as blood serum, the change in Gibbs free energies related to the mechanisms of reactions was calculated in water and n-octanol as a model for blood and lipid, respectively. The results are discussed in details in following sections.

3.2 Single electron transfer (SET)

The SET mechanism is analyzed using the following reaction [13]:

$$Cur + R^{\cdot} \rightarrow Cur^{\cdot+} + R^{-} \qquad R = {}^{\cdot}OH, {}^{\cdot}OCH_3, {}^{\cdot}OOH \text{ and } O_2^{\cdot-} \tag{1}$$

where Cur and $R^{\cdot}$ denote curcumin and examined free radicals, respectively. The Gibbs free energies for all studied species in water and n-octanol were obtained by sum of the gas-phase Gibbs energy and solvation energy for the studied species. As shown in Table 1, although the change in Gibbs free energy of reaction (1) for hydroxyl radical ($^{\cdot}OH$) is lower than other radicals, it is still a positive value. Only, in case of ($^{\cdot}OH$) in water, the value is negative because of high solvation energy of anion hydroxyl.

It should be noted that for the case of $O_2^{\cdot-}$, there are two possible reactions for SET mechanism [29]:

$$Cur + O_2^{\cdot-} \rightarrow Cur^{\cdot+} + O_2^{\cdot 2-} \tag{2}$$

$$Cur + O_2^{\cdot-} \rightarrow Cur^{\cdot-} + O_2 \tag{3}$$

where $O_2^{\cdot-}$ radical is an electron acceptor and donor in reaction (2) and (3), respectively [29]. We found out that ΔG° for both reactions (2) and (3) are positive in the gas phase, water and n-octanol. Therefore, the SET mechanism is not favorable, thermodynamically.

3.3 Radical adduct formation (RAF)

We have also investigated RAF mechanism considering probable active channels of curcumin [13]:

$$Cur + R^{\cdot} \rightarrow [Cur\text{-}R]^{\cdot} \tag{4}$$

Table 1 Change in Gibbs free energies (kJ mol^{-1}) for the single electron transfer (SET), radical adduct formation (RAF), sequential proton loss electron transfer (SPLET) and hydrogen atom transfer (HAT) processes in the gas phase, water and n-octanol

	$^{\cdot}OH$			$^{\cdot}OCH_3$			$^{\cdot}OOH$			$O_2^{\cdot-}$		
	Gas	Water	n-octanol	Gas	Water	n-octanol	Gas	Water	n-octanol	Gas	Water	n-octanol
SET	517.2	−49.6	22.5	545.6	64.2	122.3	591.0	69.7	135.6	1382.2	140.3	300.4
RAF												
c1	−101.1	−87.5	−90.7	−46.8	−37.1	−38.5	21.9	27.5	30.5	−69.8	66.3	94.2
c2	−78.3	−80.7	−81.3	−9.5	−12.8	−12.3	43.9	42.9	46.1	21.8	101.6	148.9
c3	−35.9	−41.0	−43.7	28.2	21.9	22.9	84.2	81.9	86.3	–	–	–
c4	−87.9	−85.7	−86.8	−28.0	−37.0	−33.7	29.9	41.7	43.3	−54.3	75.0	95.5
c5	14.5	17.1	15.2	75.4	76.6	76.5	146.0	145.1	149.4	–	–	–
c6	−100.2	−86.2	−90.1	−36.4	−23.2	−25.9	14.3	30.0	30.0	23.9	86.3	141.5
c7	−95.4	−81.8	−82.7	−18.1	−14.5	−13.6	44.9	42.5	47.9	−43.9	358.4	119.2
SPLET	116.4	−134.2	−98.9	144.8	−20.4	1.0	190.1	−14.9	14.2	981.4	828.5	655.5
HAT	−150.3	−175.1	−172.2	−81.7	−104.5	−100.9	−7.5	−30.5	−25.4	89.1	34.8	51.0

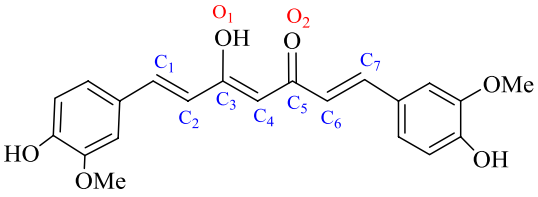

Fig. 2 Active sites of curcumin for RAF mechanism

In this work, seven sites including carbon atoms of the chain have been examined for adducting process (Fig. 2). Two oxygen atoms of enol and carbonyl moiety (O_1 and O_2, Fig. 2) were also considered. Since geometry optimization showed that the products of radicals with these two oxygen atoms were not stable, these two sites have been ruled out. The positions of C1 and C2 are approximately similar to C7 and C6, and also C3 is similar to C5. It is worth noting that the carbon atoms of C1, C2 and C3 are close to enolic hydroxyl group while C5, C6 and C7 are adjacent to an oxygen with double bond. All Gibbs free energies of RAF reactions ($\Delta G°$) for studied sites are calculated, and the results are presented in Table 1. The values that correspond to addition of $^{\cdot}OH$, $^{\cdot}OCH_3$ and $O_2^{\cdot-}$ radicals to C_1 and C_7 are close to one another. All carbons are favorite cites to be attacked by radicals except C_5 for which the values are positive. As shown in Table 1, C1 and C3 are slightly better sites to react with radicals than C7 and C5, respectively. In both solutions, C1, C4 and C6 are the most favorite sites in the chain with the most negative values for the change in Gibbs free energies. The values of $\Delta G°$ for reactions of curcumin with $^{\cdot}OH$ and other ROS radicals show that the ability of curcumin to scavenge hydroxyl radical is higher than that with other studied radicals based on RAF mechanism. The change in Gibbs free energies due to adding $^{\cdot}OOH$ and $O_2^{\cdot-}$ is positive in water and n-octanol for studied channels. Therefore, radical adducting formation process will be ruled out for these radicals. In general, the RAF process for $^{\cdot}OH$ and $^{\cdot}OCH_3$ is thermodynamically possible.

3.4 Sequential proton loss electron transfer (SPLET)

SPLET mechanism is favored in polar environments, which has been suggested by Litwinienko and Ingold [13].

$$\text{Cur-OH} \rightarrow \text{Cur-O}^- + \text{H}^+ \quad \text{(I)}$$

$$\text{Cur-O}^- + \text{R}^{\cdot} \rightarrow \text{Cur-O}^{\cdot} + \text{R}^- \quad \text{(II)}$$

$$\text{Cur-O}^{\cdot} \rightarrow \text{Cur-O}^{\cdot-} + \text{H}^+ \quad \text{(III)}$$

As suggested in this mechanism, the deprotonation step is followed by single electron transfer in reaction with free radicals and at the third step, another deprotonation process occurred. For the first deprotonation process, there are three hydroxyl groups in curcumin which can be ionized (see Fig. 3). Based on our previous study [26], the difference of Gibbs free energy between *a2* and *a3* (see Fig. 3) is smaller than the difference between *b2* and *b3*. Therefore, the change in Gibbs free energy of reaction (II) for conversion of *a2–b2* is more favorable among all possible cases. It is noteworthy that as reported previously [13], SPLET mechanism is favored in polar environments. We also found that for all studied radicals, the change in energies in water is more negative than those in n-octanol.

3.5 Hydrogen atom transfer (HAT)

In order to evaluate the radical scavenging activity of curcumin, we also considered the HAT mechanism [13].

$$\text{Cur-OH} + \text{R}^{\cdot} \rightarrow \text{Cur-O}^{\cdot} + \text{R-H} \quad (5)$$

For this purpose, we have examined the enolic and two phenolic hydroxyl groups (Fig. 3). The activities of two phenolic hydroxyl groups are almost the same; however, *b2* radical is slightly more stable than *b1* (see Fig. 3 for the chemical structures). Overall, the phenolic hydroxyl groups are better sites than the enolic hydroxyl group. This result is also in agreement with a previous reported study [12].

According to reaction (5), RH forms for $^{\cdot}OH$, $^{\cdot}OCH_3$, $^{\cdot}OOH$ and $O_2^{\cdot-}$ are H_2O, $HOCH_3$, H_2O_2 and HO_2^-, respectively. The positive ($\Delta G°$) values in Table 1 demonstrate that curcumin can scavenge all these ROS by HAT pathway. Comparison between the results also reveals that the capability of curcumin to neutralize hydroxyl radical is more than for other reactive oxygen species. In all HAT reactions between studied ROS and curcumin (reaction 5), Cur-OH and Cur-O$^{\cdot}$ species are identical; thus, Gibbs free energy for the conversion of R$^{\cdot}$ to R–H is responsible for the increase in Gibbs free energy of total reaction. This means that solvation process plays an important role in scavenging of radicals. The comparison between the change in Gibbs energies of SPLET and HAT processes show that HAT mechanism

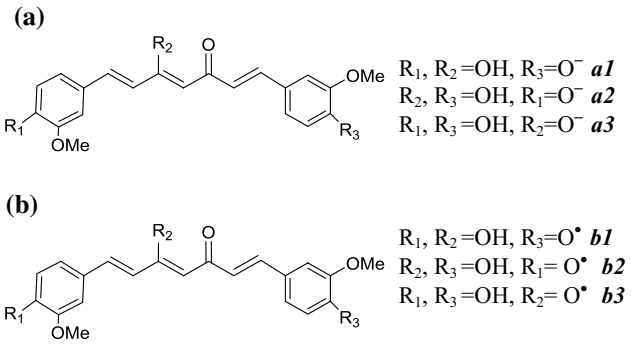

Fig. 3 **a** Deprotonated structures of curcumin. **b** Radical forms of curcumin

is thermodynamically preferred. Besides, curcumin is a weak acid with a pK_a value of 9 and the ratio of [Cur-O$^-$]/[Cur-OH] is 0.01 at neutral pH; therefore, the probability of SPLET mechanism is insignificant. All these results confirm that the HAT process can be introduced as the main probable mechanism.

3.6 Radical stabilization energy (RSE)

Radical stabilization energies (RSEs) and bond dissociation enthalpies (BDEs) are two expedient parameters that can be used for the prediction and interpretation of reactions in free radical chemistry [30]. Determination of stabilization energy is not directly practical, and it should be obtained indirectly from the results of kinetic, thermochemical or electrochemical experiments [30]. The theoretical prediction of thermodynamic stabilities is specifically attractive because it makes the direct comparison of radicals of widely different electronic characteristics and structures [31]. The thermodynamic stability is in general related to an arbitrarily chosen reference system [31]. The stability of radicals can be defined relative to reference systems sharing the same type of radical center. Methyl and hydroxyl radicals are the most obvious choices for carbon-centered and oxygen-centered radicals, respectively [32]. With these references, the "radical stabilization energy" is the changes in enthalpies for the following reactions [31]:

$$^{\cdot}CH_3 + \text{R-H} \rightarrow CH_4 + R^{\cdot} \quad (6)$$

$$^{\cdot}OH + \text{R-OH} \rightarrow H_2O + \text{R-O}^{\cdot} \quad (7)$$

The stability of oxygen-centered radicals also resulted in quantitative description of antioxidant activity [31]. These reactions are classified as hydrogen atom transfer (HAT) process [32].

The theoretical calculations for curcumin and vitamin C show that RSE of curcumin is significantly high (−136.5 kJ mol^{-1}) and is comparable with vitamin C (−141.4 kJ mol^{-1}). Therefore, curcumin can be considered a potent antioxidant as commendable as vitamin C. The details of calculations for radical stabilities of studied radicals are included in Supporting Information, Table S9 and S10. It is worth nothing that the RSE related to phenolic hydroxyl group is much greater than the RSE of the middle –CH_2– group in the diketo form of curcumin (−136.5 vs. −32.3 kJ mol^{-1}). These values suggest that the phenolic hydroxyl group is responsible for the radical-trapping activity of curcumin.

In continuation of this study, we also calculated the RSE of some related compounds such as bis-demethoxycurcumin (BDMC), demethoxycurcumin (DMC) and tetrahydrocurcumin (THC) as the important metabolite of curcumin (Fig. 4a, c). The results are summarized in Table 2. As

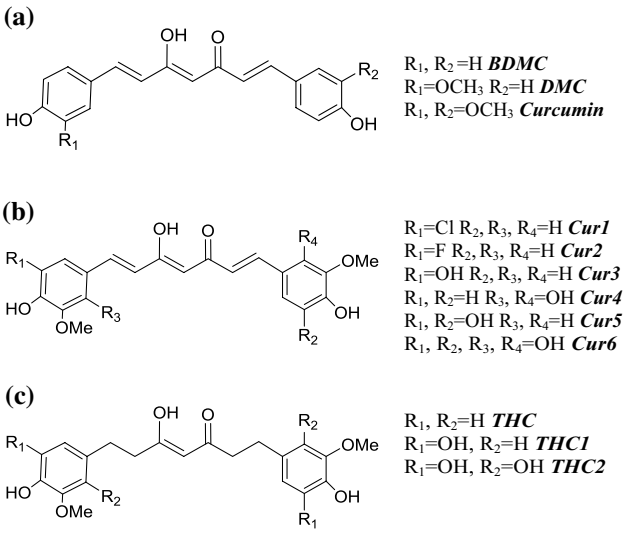

Fig. 4 **a** and **b** curcumin and some of its derivatives. **c** Tetrahydrocurcumin (THC) and two of its derivatives

Table 2 Radical stabilization energies (RSEs) calculated at the level of BMK/6-311+G(d,p) and solvation energies (kJ mol^{-1}) of curcumin, THC and their derivatives (see Fig. 4)

	Species	RSE	ΔG_{solv}
Curcumin and its derivatives	BDMC	−138.1	−81.2
	DMC	−136.5	−74.7
	Curcumin	−136.5	−66.6
	Cur1	−141.1	−68.4
	Cur2	−143.1	−66.0
	Cur3	−165.6	−76.2
	Cur4	−153.7	−94.4
	Cur5	−165.5	−85.1
	Cur6	−185.5	−118.0
THC and its derivatives	THC	−129.8	−64.8
	THC1	−160.2	−82.3
	THC2	−180.4	−112.2

shown in this table, demethoxy and bis-demethoxy curcumin are also suitable radical scavengers (−136.5 and −138.1 kJ mol^{-1}). However, the comparison of RSEs of curcumin and THC (−136.5 vs. −129.8 kJ mol^{-1}) suggests that the antioxidant activity of curcumin is higher than THC.

Since high metabolism and poor solubility are two major factors that limit the bioactivities of curcumin [33], change in its structure by means of different substituents is a worthy strategy to improve the activity of curcumin. For this aim, we investigated several derivatives of curcumin that included OH, F and Cl as substituent (Fig. 4b). Since the values of RSE for derivatives with OH substituent (*Cur3*–*Cur6*) are

considerably increased, these species show more radical scavenging activity compared to curcumin. The results in Table 2 clearly show that the solvation energies for derivatives of *Cur3–Cur6* are also increased; therefore, these derivatives should have better solubility in aqueous solution. These conclusions are also true for THC. As a result, *Cur6* and THC2 have better solubility and the higher ability to scavenge free radicals.

4 Conclusions

In this study, the chemical structures of curcumin in terms of enol–diketo tautomerism have been investigated theoretically. The enol form has been found the dominant form of curcumin. We also studied all probable mechanisms such as hydrogen atom transfer (HAT), single electron transfer (SET), radical adduct formation (RAF) and sequential proton loss electron transfer (SPLET) of curcumin with reactive oxygen species (ROS) in solutions of water and n-octanol. Our results revealed that curcumin can scavenge ˙OH better than other ROS. We also found out HAT mechanism is thermodynamically more favored than other studied mechanisms. Radical stabilization energies (RSEs) of curcumin and some of its derivatives as well as vitamin C have been calculated, and the results showed that the antioxidant activity of curcumin is as high as vitamin C. This study also suggested that the presence of extra OH groups increased the potential of antioxidant activity and the solubility of curcumin considerably.

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