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DFT study on the synergistic effect of antioxidant and lipid solubility of catechins with structural modification

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With the aid of density functional theory (DFT), the optimized structures of catechins and their derivatives have been obtained. The synergistic effect of antioxidant and lipid solubility has also been explored with the analysis of the thermodynamics enthalpies of the hydrogen abstraction reaction with DPPH and the spin densities of radical products. It is concluded that the structure modifying on the phenolic hydroxyl site of EGCG results in the pronounced electron delocalization and the enhancement of product free radical stability, leading to a significant improvement in antioxidant activity. Furthermore, the structure modification significantly reduces molecular polarity and enhances the lipid solubility of catechins and their derivatives, resulting in a synergistic effect between antioxidant activity and lipid solubility. On this basis, the effects of solvent polarity differences on the antioxidant activity and lipid solubility of catechins and their derivatives have been analyzed. It is suggested that differences in solvent polarity primarily influences the relative strength of antioxidant activity and lipid solubility at different sites, but does not alter the highest activity sites and the positive impact of structural modification on both antioxidant and lipid solubility.

Keywords: Catechins, Antioxidant, Lipid solubility, Solvent polarity, Density functional theory

Epicatechin (EC), epigallocatechin gallate (EGC), epicatechin gallate (ECG), and epicatechin cholate (EGC) are the primary components of catechins. Notably, epigallocatechin gallate (EGCG) is particularly significant in tea due to its potent antioxidant activity [1] and its various pharmacological effects, including anti-tumor, anti-inflammatory, anti-aging, and antiviral properties. However, its poor lipid solubility due to the presence of multiple hydroxyl groups limits its application in the study of antioxidant properties within lipid systems [2].

In recent years, many studies have suggested that structurally modifying EGCG to improve its lipid solubility while preserving its biological activities and expanding its application scope has emerged as a significant research direction [3,4,5]. Current experimental studies commonly employ acylation reactions on the phenolic hydroxyl and aromatic ring structures of EGCG, primarily through two approaches: oxygen acylation *via* esterification and carbon acylation *via* Friedel-Crafts acylation [6,7,8]. For example, Yang [9] reported that esterified EGCG acetate demonstrated improved stability and increased efficacy in inhibiting HIV. Lu[10] and their colleagues found that structurally modified EGCG derivatives displayed significantly higher antioxidant activity, with a positive correlation observed between their antioxidant efficacy and lipid solubility. Nonetheless, most of these experimental investigations focus on differences in antioxidant activity and the intrinsic mechanisms of catechins' antioxidant activity and lipid solubility have not been explored in depth at the molecular level. The constraints associated with individual experimental methodologies highlight the necessity for a theoretical framework to clarify the structural regulatory elements and fundamental principles that influence the synergistic improvement of antioxidant activity and lipid solubility, both prior to and following structural modifications.

The advancement of quantum chemical calculations has offered a practical methodology for tackling these challenges. For example, Gao[12] and co-workers used quantum chemical calculations to study the antioxidant synergism between resveratrol and sesamol in oils; Liu[13] analyzed the interaction between characteristic structural units of persimmon tannin and metal ions as well as their antioxidant activity through computational methods; Pang[14] conducted experimental and theoretical studies on composite materials; Li[15] and co-workers synthesized berberine C(9)-lipoic acid esters and performed quantum chemical calculations—all of which demonstrate the reliability and application of quantum chemical methods. Accordingly, density functional theory (DFT) demonstrates a significant level of accuracy in studying the antioxidant activity of polyphenolic compounds[15,16,17]. In this context, theoretical calculation method was chosen to elucidate the intrinsic mechanisms of the synergistic effect of structural modification on the antioxidant activity and lipid solubility of catechins at the molecular level.

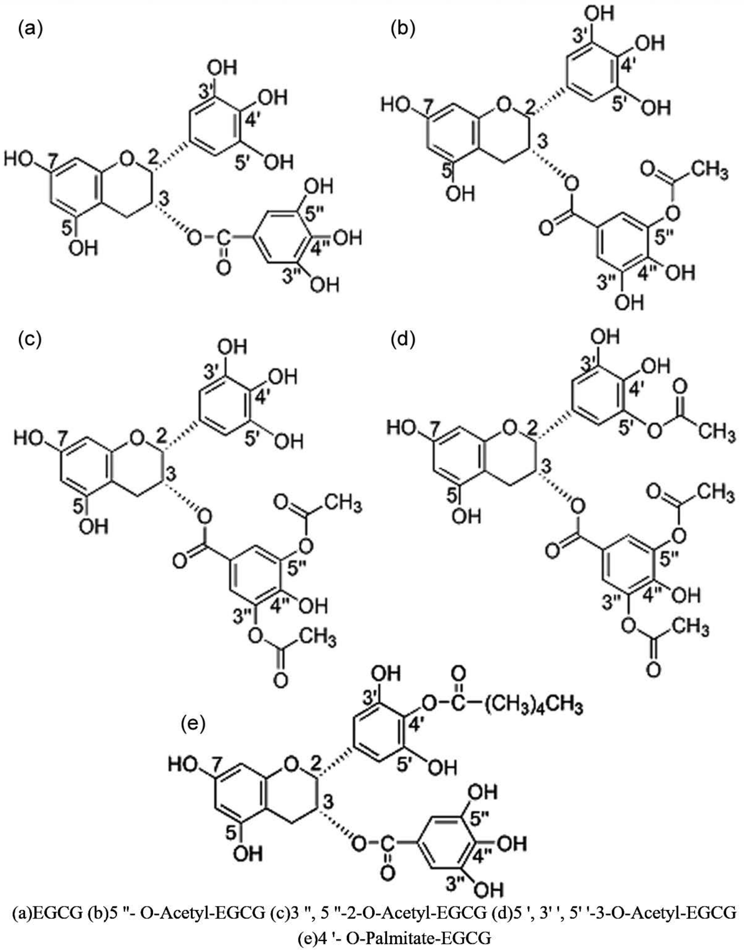
Method of calculation

All calculations in this study were performed using Gaussian 09 (Ref. 18). Given the advantages of the M06-2X method[19] for modeling weak molecular interactions, geometry optimizations were conducted at the M06-2X/6-31G(d) level, utilizing acetone and benzene as solvents and employing the SMD[20] solvation model. Frequency calculations confirmed the ground-state nature of the compounds, as indicated by the absence of imaginary frequencies. The reaction enthalpy values under solvent conditions were calculated at standard state (1 mol/L, 298 K).

Results and Discussion

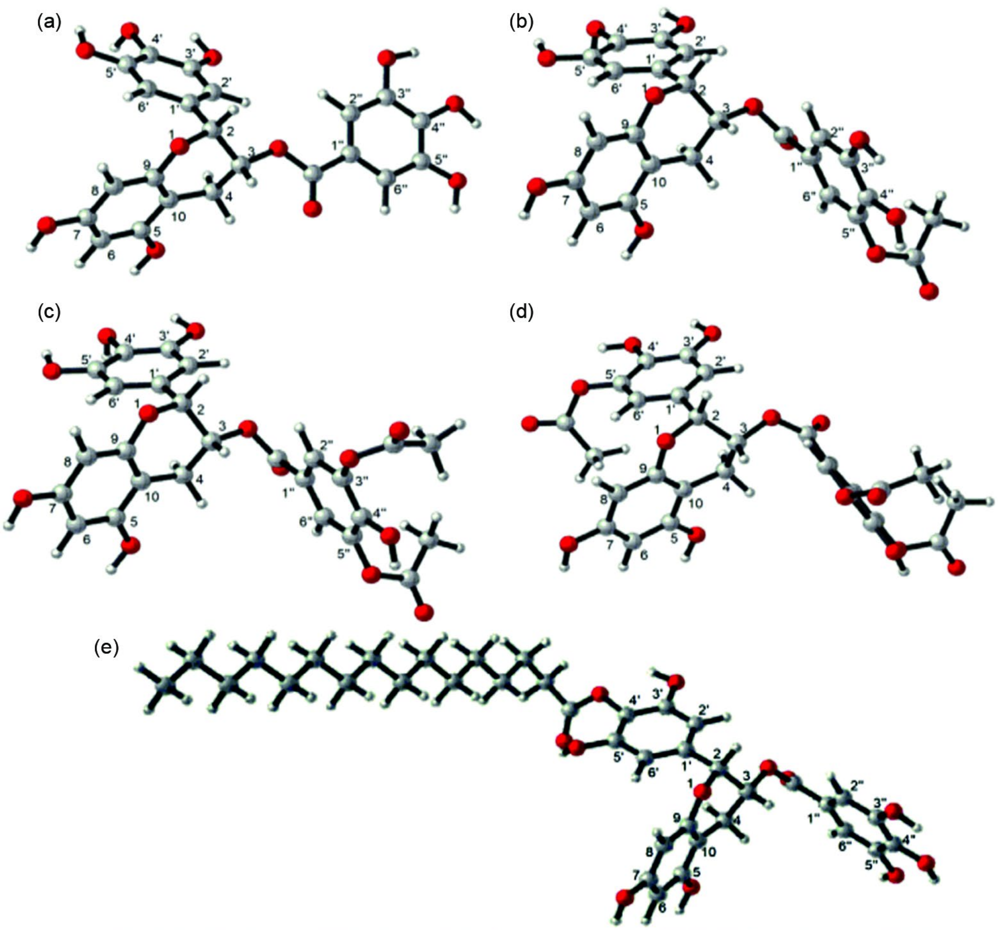
Structural optimization of EGCG and its derivatives

This research builds upon earlier experimental studies and focuses on specific EGCG oxoacylated derivatives as the subject of analysis. To elucidate the structural changes, we made targeted substitutions at the 5"、3", 5"、 5', 3", 5"and 4' phenolic hydroxyl positions of EGCG, resulting in the creation of four derivatives: 5"-O-acetyl-EGCG (b), 3"-5"-di-O-acetyl-EGCG (c), 5'-3"-5"-tri-O-acetyl-EGCG (d), and 4'-O-palmitate-EGCG (e). The original compound, EGCG, is labeled as (a) in Fig. 1. Through computational simulations, we identified the most stable optimized structures for each molecule, as illustrated in Fig. 2.



(a)EGCG (b)5 "- O-Acetyl-EGCG (c)3 ", 5 "-2-O-Acetyl-EGCG (d)5 ', 3' ', 5' '-3-O-Acetyl-EGCG
(e)4 '- O-Palmitate-EGCG

Fig. 1 — Molecular structure diagrams of five catechin compounds



(a) EGCG (b) 5 '' - O-Acetyl-EGCG (c) 3 '', 5 '-2-O-Acetyl-EGCG (d) 5', 3 '', 5 '-3-O-Acetyl-EGCG

(e) 4' - O-Palmitate EGCG

Fig. 2 — Optimization structure diagram of five catechin compounds

Table 1 — Enthalpy of hydrogen evolution reaction of EGCG and its derivatives in gas phase ($\Delta H_{f,}$ unit: kcal/mol)

Hydroxyl sites	a	b	c	d	e
C_7-OH	21.63	22.34	22.53	23.39	22.18
C_3'-OH	11.63	12.26	12.48	23.74	23.21
C_4'-OH	4.15	5.24	5.28	15.72	
C_5'-OH	20.00	12.80	13.20		23.48
C_3''-OH	33.50	24.97			24.64
C_4''-OH	22.85	15.75	21.28	21.24	16.11
C_5''-OH	34.72				17.48

Note: Blank means that there is no phenolic hydroxyl site

Quantum chemistry study on the antioxidant properties of catechin and its structurally modified derivatives

Thermodynamic analysis of hydrogen extraction reactions

The magnitude of enthalpy is a thermodynamic parameter used to evaluate the ease with which catechins can accept hydrogen in the hydrogen atom transfer (HAT) mechanism[21,22,23,24,25,26]. Catechins react with DPPH radicals to abstract a hydrogen atom from DPPH, resulting in the formation of catechin radicals and $DPPH_2$[27,28,29]. In this study, the M06-2X/6-31G(d) method was employed for optimized calculations of enthalpy for catechins, radicals, DPPH, and $DPPH_2$ in the gas phase, yielding the data presented in Table 1. Due to the varying positions of

Table 2 — Spin density values of optimized gas phase EGCG and derivatives

Hydroxyl sites	a	b	c	d	e
C_5-OH	0.654	0.656	0.387	0.390	0.618
C_7-OH	0.688	0.681	0.420	0.420	0.639
C_3'-OH	0.827	0.673	0.383	0.422	0.404
C_4'-OH	0.588	0.573	0.376	0.380	
C_5'-OH	0.680	0.680	0.387		0.643
C_3'-OH	0.677	0.679			0.426
C_4''-OH	0.662	0.601	0.382	0.382	0.381
C_5''-OH	0.896				0.397

phenolic hydroxyl groups, the ease of hydrogen abstraction differs. The magnitude of enthalpy at the same phenolic hydroxyl site indicates the strength of catechins' ability to scavenge DPPH radicals; a smaller value signifies that the hydrogen abstraction reaction occurs more readily, indicating a stronger capacity to scavenge DPPH radicals. Additionally, the number of phenolic hydroxyl groups must be taken into account. Through comparative analysis in Table 1, it can be observed that:

The $C_{4'}$-OH group of compounds a, b, c, and d exhibits the lowest enthalpy among all phenolic hydroxyl sites in their respective structures, indicating that the C4' site serves as the primary antioxidant activity site for EGCG and is the most active antioxidant site for compounds b, c, and d. In contrast, compound e lacks a $C_{4'}$-OH group, resulting in its $C_{4''}$-OH enthalpy being the lowest, which suggests that the $C_{4''}$ site is the most significant antioxidant active site for compound e. These results demonstrate that, following structural modifications, the primary antioxidant active site for EGCG derivatives is the $C_{4'}$ position.

Compared to compound a, compound b exhibits significantly lower enthalpy at the C_5-OH, $C_{5'}$-OH, $C_{3''}$-OH, and $C_{4''}$-OH phenolic hydroxyl sites. The enthalpy at other phenolic hydroxyl sites shows minimal variation, suggesting that compound b possesses stronger antioxidant activity than compound a. Similarly, compounds c, d, and e also demonstrate greater antioxidant activity than compound a. Based on a comprehensive analysis of EGCG and its five derivatives, the order of antioxidant activity is as follows: compound b > compound c > compound e > compound d > compound a.

Spin density analysis

Spin density refers to the distribution of unpaired electrons in oxygen (O) atoms. The spin density values of O atoms in EGCG and its derivative phenolic hydroxyl groups were analyzed. A smaller value indicates a more uniform distribution, greater stability of free radicals, and enhanced antioxidant properties[30,31]. Please refer to Table 2 for further details.

(1) The spin density values of the $C_{4'}$-OH in the phenolic hydroxyl groups of compounds a, b, c, and d are the lowest. In contrast, since compound e lacks a $C_{4'}$-OH group, its spin density value at the $C_{4''}$ position is the lowest overall. Consequently, the $C_{4'}$ position exhibits the highest antioxidant activity for compounds a, b, c, and d, while the $C_{4''}$ position demonstrates the highest antioxidant activity for compound e. These results indicate that after the structural modification of EGCG, the primary antioxidant active site is the $C_{4'}$ position.

(2) Compound b and compound a both exhibit spin density values at the hydroxyl site ranging from 0.573 to 0.827. At the C_7-OH, $C_{3'}$-OH, $C_{4'}$-OH, and $C_{4''}$-OH sites, the spin density value of compound b is lower than that of compound a, while the spin density values at other sites do not show significant differences. This suggests that compound b possesses stronger antioxidant properties than compound a. Similarly, compared to compound a, compounds c, d, and e demonstrate lower spin densities at each site. However, their antioxidant effects remain stronger than those of compound a, although they may be weaker than those of compound b.

Analysis of the influence of structural modification on antioxidant activity

From the previous analysis, the order of antioxidant activity was determined as follows: compound b> compound c> compound e> compound d> compound a. Furthermore, structural modifications were found to influence antioxidant properties; EGCG derivatives with altered structures demonstrate stronger antioxidant activity than EGCG, indicating consistent analytical patterns. Based on spin density analysis, we

Table 3 — Polar moment of EGCG and derivatives optimized in acetone solvent phase

Chemical compound	a	b	c	d	e
Dipole moment	8.2330	3.7227	6.6843	5.8100	6.4530

Table 4 — Dipole moments of EGCG and its derivatives in various solvents

Chemical compound	a	b	c	d	e
Organic solvent					
Acetone	8.2330	3.7227	6.6843	5.8100	6.4530
Benzene	6.8017	3.2261	5.8973	5.0768	5.4661

Table 5 — Optimized Gibbs free energy (ΔG, kcal/mol) of EGCG and its derivatives in various solvents

Hydroxyl sites	a		b		c		d		e	
	acetone	benzene	acetone	benzene	acetone	benzene	acetone	benzene	acetone	benzene
C_5-OH	27.81	30.78	6.22	8.99	5.76	8.82	7.39	9.40	27.99	30.47
C_7-OH	27.68	30.85	6.99	10.24	7.27	10.01	7.50	9.93	27.60	30.01
C_3'-OH	29.79	33.12	–1.19	0.75	–1.03	2.23	6.77	8.44	5.54	10.16
C_4'-OH	–7.53	–5.22	–7.39	–6.24	–7.52	–6.18	0.80	3.14		
C_5'-OH	29.38	32.44	–0.15	1.15	–0.65	1.03			30.00	31.03
C_3''-OH	6.69	13.60	7.60	11.85					6.67	11.01
C_4''-OH	0.22	5.30	0.078	3.89	4.86	7.28	5.95	8.65	–0.40	3.85
C_5''-OH	3.64	7.40							3.05	5.69

Note: Blank means that there is no phenolic hydroxyl site

propose that molecular structural modifications lead to increased electron dispersion at the oxygen atom of the hydroxyl group in the semiquinone radical, resulting in more pronounced electron delocalization and enhanced stability of the radical, thereby improving antioxidant activity.

Quantum chemistry study on the lipophilicity of catechins and its structurally modified derivatives

In this study, the M06-2X/6-31G(d) method was employed to optimize the calculation of the dipole moment of catechin and its structurally modified derivatives in acetone solvent. Table 3 presents data indicating that the dipole moment of compound a was greater than that of compounds b, c, d, and e, suggesting that the lipophilicity of the EGCG derivatives is higher than that of the parent EGCG compound.

Effect of solvent polarity on antioxidant activity and lipophilicity

Effect of solvent polarity on lipophilicity

To the best of our knowledge, this study systematically investigates the effects of solvents with varying polarities (acetone > benzene) on the lipophilicity of structurally modified catechins. According to Table 4:

(1) The dipole moments of compounds a, b, c, d, and e exhibit a decreasing trend. The results indicate that lipophilicity decreases with increasing solvent polarity. This phenomenon can be attributed to the lower polarity of the derivatives, which demonstrate enhanced solubility in solvents with reduced polarity. In other words, the closer the polarity of the solvent is to that of the catechin derivatives, the more pronounced the enhancement of lipophilicity.

(2) Compared to compound a, compounds b, c, d, and e exhibit lower dipole moments in both acetone and nonpolar benzene solvents. This observation can be attributed to the fact that EGCG derivatives consistently demonstrate higher lipophilicity than EGCG in solvents of varying polarity.

Effect of solvent polarity on antioxidant activity

This study systematically compares the antioxidant activity of compounds in acetone (a polar solvent) and benzene (a nonpolar solvent) using a combination of experimental and computational approaches. The directionality of a chemical reaction is thermodynamically determined by the change in Gibbs free energy (ΔG). A lower Gibbs free energy (ΔG) at the site of the phenolic hydroxyl group correlates with enhanced DPPH radical scavenging activity, suggesting a stronger capacity for electron or hydrogen atom donation.

As demonstrated by the comparative analysis in Table 5, the Gibbs free energy (ΔG) of phenolic

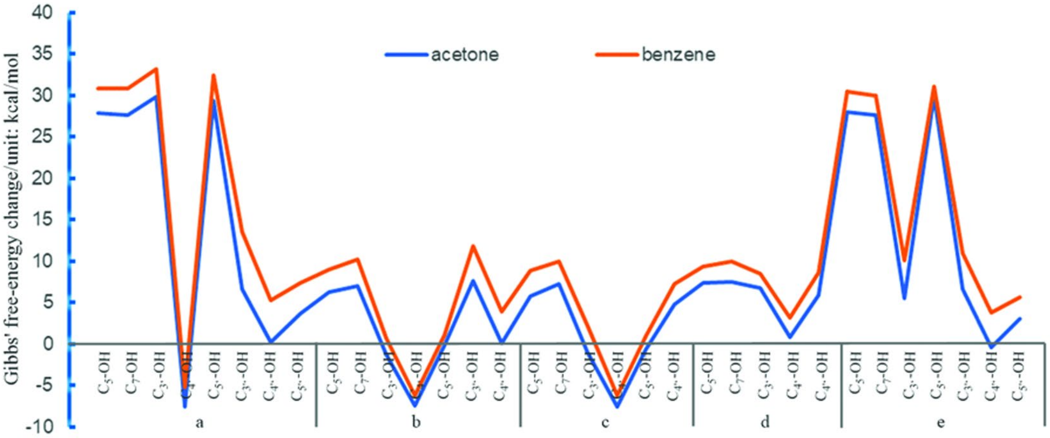


Fig. 3 — Comparison of hydrogen-bonding energy for EGCG and its derivatives in various solvents

hydroxyl groups in a given compound varies significantly with solvent polarity. A decrease in solvent polarity (acetone > benzene) correlates with increased ΔG values, which consequently diminishes antioxidant activity. This trend is further illustrated by the progressive increase in hydrogen abstraction energy across all five catechin derivatives from acetone to benzene, accompanied by a corresponding decline in antioxidant efficacy. Notably, the highest antioxidant activity is observed in acetone, consistent with its greater polarity and enhanced stabilization of transition states during radical scavenging.

To enable clearer visualization, the hydrogen abstraction energies in both solvents are plotted in Fig. 3. As clearly depicted, the green curve (representing benzene) is positioned above the red curve (representing acetone), indicating that increased solvent polarity enhances antioxidant activity in both EGCG and its derivatives. Furthermore, variations in solvent polarity do not affect the superior antioxidant activity of structurally modified EGCG derivatives compared to native EGCG, nor do they alter the localization of their primary antioxidant active sites. Solvent-phase energy analysis confirms that EGCG derivatives maintain superior antioxidant activity relative to native EGCG. The B-ring $C_{4'}$ position serves as the site of highest activity for compounds a-d, while in the absence of this site (as seen in compound e), the D-ring $C_{4''}$ position becomes the dominant active site. These results demonstrate that the B-ring $C_{4'}$ position continues to function as the primary antioxidant active site in EGCG derivatives following structural modification.

It is important to note that while we examined the influence of solvent polarity on lipophilicity and antioxidant activity in the previous text, our analysis primarily focused on two solvents: benzene and acetone, which provided a limited dataset. Nevertheless, this does not change our conclusion that antioxidant activity and lipophilicity are more pronounced in the more polar solvent, acetone. In future studies, we plan to further investigate the fundamental relationships between solvent polarity and its effects on antioxidant activity and lipophilicity.

Conclusions

In this context, with the aid of DFT, the M06-2X/6-31G(d) method was employed to perform optimization calculations on catechin EGCG, its derivatives, and corresponding radical products. Analysis of enthalpy values, spin density, Gibbs free energy, and dipole moment data was conducted. The conclusion is as follows:

(1) Antioxidant activity among the five compounds of catechin and its derivatives follows the order of 5''-O-acetyl-EGCG > 3'',5''-di-O-acetyl-EGCG > 4'-O-palmitate-EGCG > 5',3'',5''-tri-O-acetyl-EGCG > EGCG. The C4' site of the B ring serves as the most significant antioxidant active site for EGCG, 5''-O-acetyl-EGCG, 3'',5''-di-O-acetyl-EGCG, and 5',3'',5''-tri-O-acetyl-EGCG. In the absence of the B-ring $C_{4'}$ site, the $C_{4''}$ site of the D ring becomes the primary antioxidant active site for 4'-O-palmitate-EGCG. Following the structural modification of EGCG, the primary active site for antioxidants is the $C_{4'}$ site.

(2) The modified structure of catechins with different positions of phenolic hydroxyl group significantly increase the delocalization of electrons in their phenolic hydroxyl groups, which makes hydrogen atom transfer reactions easier and greatly

boosts their antioxidant effectiveness. Additionally, these modifications reduce molecular polarity, thereby greatly enhance lipid solubility. The structural modification of catechins demonstrates a synergistic effect between improved antioxidant activity and increased lipid solubility. This conclusion is consistent with the findings of previous experimental research[11].

（3）Alterations in solvent polarity do not affect the synergistic effect; however, for compounds with identical structures, increased solvent polarity is linked to decreased lipid solubility and diminished antioxidant activity. Nevertheless, these variations had minimal impact on identifying the most active sites or on the beneficial effects of structural changes on antioxidant activity and lipid solubility.

In the final analysis, this study utilized density functional theory (DFT) to investigate the synergistic effect between antioxidant activity and lipid solubility in structurally modified catechins. The antioxidant activity and lipid solubility of EGCG and its derivatives were examined in this study. The influence of solvent polarity on these characteristics was assessed. An understanding of the distinctions and mechanisms governing antioxidant activity and lipid solubility before and after the structural modification of catechins was offered. We hope that this study will provide a theoretical basis for a deeper understanding of the synergistic enhancement of antioxidant activity and lipid solubility through catechin structural modification, thereby benefiting the future development and broadening of the application scope of catechins as natural antioxidants.

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