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COMPUTATIONAL STUDY OF THE EFFECT OF STRUCTURE ON ANTIOXIDANT ACTIVITY AND DRUG SCORE OF COUMARIN DERIVATIVES

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Abstract

The presence of reactive oxygen species in the body must be maintained at low concentrations, as an excess can lead to oxidative stress. Coumarin, a secondary metabolite found in plants, exhibits potential as an antioxidant agent. However, the development of synthetic antioxidants based on coumarin remains limited. Computational studies enable the manipulation of coumarin structures to predict antioxidant activity. Correspondingly, this research aimed to investigate the effect of the type, number, and position of substituents on the antioxidant activity and drug score of coumarin derivatives utilizing computational methods, specifically ORCA and OSIRIS Property Explorer software. The results revealed that electron-donating substituents (e.g., OCH_3) could enhance antioxidant activity, while electron-withdrawing substituents (e.g., CHO) tended to reduce it. Substitution on the benzene ring of coumarin exerted a more significant effect on antioxidant activity compared to substitution on the pyrone ring. Compounds such as Umbelliferone, Scoparone, and 3-Bromoscoparone exhibited potential as new antioxidants due to their structural similarity to ascorbic acid or TBHQ. However, further studies are necessary to confirm their development as safe and effective antioxidants free from side effects.

Keywords: *antioxidant activity, coumarin derivatives, computational method, drug score, OSIRIS*

Introduction

Superoxide radical ($\cdot O_2^-$), hydroxyl radical ($\cdot OH$), peroxyl radical ($\cdot OOR$), alkoxyl radical ($\cdot OR$), nitric oxide ($NO\cdot$), hypochlorous acid (HOCl), hydrogen peroxide (H_2O_2), and singlet oxygen ($^1O_2$) are types of reactive oxygen species (ROS). The presence of ROS in the body must be maintained at low concentrations. When the level becomes excessive and the body cannot neutralize them, a condition known as oxidative stress occurs. This condition can trigger various diseases, including atherosclerosis, Alzheimer's disease, diabetes, tumors, and other illnesses. Environmental factors such as UV radiation and pollutants (e.g., heavy metals, cigarette smoke, drugs, and pesticides) significantly contribute to increased ROS levels in the body (Pizzino et al., 2017). Therefore, the body requires the intake of foods containing antioxidants to prevent, slow down, or eliminate oxidative damage to target molecules. Antioxidants can block the oxidation of other substances by directly scavenging ROS or indirectly inhibiting ROS production in the body (Gulcin, 2020).

Coumarin (1,2-benzopyrone or 2H-1-benzopyran-2-one) refers to all compounds

containing a benzene ring fused with a pyrone ring. It is a secondary metabolite of plants, characterized by its sweet aroma, similar to vanilla. The specific biological properties of coumarin and its derivatives depend on their chemical structure, particularly variations in substitution patterns. In pharmacology, coumarin is an antimicrobial, antioxidant, anti-inflammatory, anti-HIV, anticancer, anticoagulant, antiviral, and anti-tuberculosis agent. In nature, it is found in various plants, most notably in the food-flavoring cinnamon bark. Despite its numerous health benefits, excessive doses above 0.1 mg/kg body weight per day can cause hepatotoxic effects (Lončar et al., 2020). Nearly 1300 coumarin derivatives have been identified, mainly as secondary metabolites in plants, fungi, and bacteria (Fylaktakidou et al., 2004).

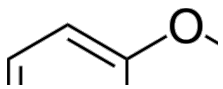


Figure 1. Simple molecular structure of coumarin (Lončar et al., 2020)

Several coumarin derivatives act as antioxidants due to their ability to interact with ROS. Coumarins substituted with a hydroxyl group on the benzene ring are more effective ▪OH radical scavengers compared to those substituted on the pyrone ring or to unsubstituted coumarins. The scavenging efficiency follows this order: 7-Hydroxycoumarin > 4-Hydroxycoumarin > Coumarin. Moreover, coumarins substituted with methyl and methoxy groups on the benzene ring are superior ▪OH radical scavengers compared to those substituted with hydroxyl groups on the pyrone ring. The order of activity is 7-Methoxycoumarin > 7-Hydroxycoumarin > 7-Methylcoumarin > 4-Hydroxycoumarin. Additionally, coumarins with two hydroxyl groups on the benzene ring exhibit distinct properties. For example, coumarins substituted with two hydroxyl groups at the ortho position (o-dihydroxycoumarins), such as 6,7-Dihydroxy-4-Methylcoumarin, can act as pro-oxidants. In contrast, when substituted at the meta or para positions, such as 5,7-Dihydroxy-4-Methylcoumarin, they function as ▪OH scavengers (Payá et al., 1992).

The antioxidant activity of coumarin in scavenging free radicals involves several mechanistic processes: (1) Hydrogen Atom Transfer (HAT) and (2) Single Electron Transfer (SET). In the direct HAT process, the reaction is represented as $ROO\bullet + ArOH \rightarrow ROOH + ArO\bullet$, focusing on the O-H Bond Dissociation Enthalpy (BDE). The formula for O-H BDE is given as O-H BDE = Hr + Hh – Hp, where Hr is the radical enthalpy, Hh is the enthalpy of the H atom (-0.49792 Eh), and Hp is the enthalpy of the parent molecule. In the electron and proton transfer process, represented as $ROO\bullet + ArOH \rightarrow ROO^{-} + ArOH\bullet^{+} \rightarrow ROOH + ArO\bullet$, the focus is on the Adiabatic Ionization Potential (IP). The formula for IP is IP = (TEc + TCEc × 0.9805) - (TEp + TCEp × 0.9805), where TEc is the total energy of the radical cation, TCEc is the total energy correction for the radical cation, TEp is the total energy of the parent molecule, and TCEp is the total energy correction for the parent molecule (Zhang & Wang, 2004). Antioxidant activity refers to the reaction rate constant between an antioxidant and a specific oxidant. Meanwhile, antioxidant capacity measures the total amount of free radicals that can be scavenged (MacDonald-Wicks et al., 2006).

The reactivity and antioxidant activity of coumarin derivatives can be evaluated based on parameters such as HOMO energy values, energy gaps, O-H BDE, and IP through computational calculations using ORCA software. Experimentally, methods employed for studying HAT mechanisms include ORAC (Oxygen Radical Absorbance Capacity), TRAP (Total Radical Trapping Antioxidant Parameter), TOSCA (Total Radical Scavenging Capacity Assay), and others (Huang et al., 2005). For SET mechanisms, methods such as TEAC (Trolox Equivalence Antioxidant Capacity), FRAP (Ferric Ion Reducing Antioxidant Power), and DPPH (2,2-Diphenyl-1-Picrylhydrazyl Radical Scavenging Assay) are commonly used (Gulcin, 2020). Meanwhile, the ABTS (2,2-Azinobis 3-Ethylbenzthiazoline-6-

Sulfonic Acid Radical Scavenging Assay) method suits both HAT and SET mechanisms.

The drug score of a compound combines several factors, including drug similarity, partition coefficient (cLog P), solubility (Log S), molecular weight, and toxicity risk. The cLog P value, the logarithm of the partition coefficient between n-octanol and water, measures the compound's hydrophilicity; higher cLog P values indicate lower hydrophilicity and poor absorption. The Log S value represents the logarithm of solubility, helping to avoid compounds with poor solubility, which can significantly affect permeation and distribution. Molecular weight also affects absorption, as larger molecular weights are typically associated with lower absorption and challenges in reaching the target site. Drug similarity is determined by molecular fragments commonly found in commercial drugs, while toxicity risk is assessed by identifying fragments associated with mutagenic, tumorigenic, irritant, and reproductive effects (Wulandari et al., 2020). Drug scores can be determined through computational calculations using OSIRIS Property Explorer software, based on physicochemical properties such as log P, log S, molecular weight, drug similarity, and toxicity risk.

Given the above considerations, investigating the free radical scavenging ability of various coumarin derivatives is crucial. This secondary metabolite holds significant potential as an antioxidant supplement in the future. Accordingly, the present study involved a computational analysis of the effect of molecular structure on the antioxidant activity and drug score of coumarin derivatives using ORCA and OSIRIS Property Explorer software. The objective was to identify the effect of the number, type, and position of substituents on coumarin compounds concerning their antioxidant activity and drug score.

Methodology

The materials used in this study included 12 coumarin derivative molecular models, as shown in Table 1, along with positive control compounds: ascorbic acid (vitamin C) and tert-butylhydroquinone (TBHQ). The equipment consisted of Avogadro 4.2.1 software for molecular visualization, ORCA 5.0 for computational calculations, OSIRIS Property Explorer for drug score analysis, Minitab 21 for statistical analysis, and Python 3.13 for calculating the Tanimoto coefficient.

The three-dimensional (3D) structural models of the coumarin derivatives (see Table 1) were created using Avogadro software. These derivatives then underwent molecular geometry optimization, minimizing molecular energy to achieve the most stable structural conformation. Computational calculations were performed using the B3LYP method with the def2-SVP basis set in ORCA software. The commands used were:

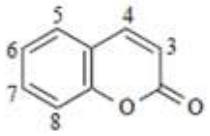
!B3LYP D4 def2-SVP Opt Normalprint Printbasis PrintMOs
!B3LYP D4 def2-SVP NumFreq

The first command provided data on HOMO energy and the energy gap. The optimized molecular structures were subjected to numerical frequency calculations using the second command, yielding the total electronic energy, thermal correction, and enthalpy for each state of the coumarin derivatives. Simple mathematical calculations were then performed using the following formulas:

$IP=(TE_c + TCE_c \times 0.9805) - (TE_p + TCE_p \times 0.9805$ and OH $BDE= H_r + H_h - H_p)$

The toxicity and drug score of the coumarin derivatives were determined based on their molecular structures using OSIRIS Property Explorer software. The data obtained included cLog P, Log S, molecular weight, TPSA, drug-likeness, toxicity risks, and drug score.

Table 1. Investigated coumarin derivatives



No.	Molecules	R3	R4	R5	R6	R7	R8
1	Coumarin	H	H	H	H	H	H
2	4-Hydroxycoumarin	H	OH	H	H	H	H
3	7-Hydroxycoumarin (Umbelliferone)	H	H	H	H	OH	H
4	7-Methoxycoumarin (Herniarin)	H	H	H	H	OMe	H
5	7-Methylcoumarin	H	H	H	H	Me	H
6	7-Formylcoumarin	H	H	H	H	CHO	H
7	3-Methylscoparone	CH_3	H	H	OMe	OMe	H
8	3-Bromoscoparone	Br	H	H	OMe	OMe	H
9	3-Formylscoparone	CHO	H	H	OMe	OMe	H
10	6,7-Dihydroxycoumarin (Esculetin)	H	H	H	OH	OH	H
11	7-Hydroxy-6-Methoxycoumarin (Scopoletin)	H	H	H	OMe	OH	H
12	6,7-Dimethoxycoumarin (Scoparone)	H	H	H	OMe	OMe	H

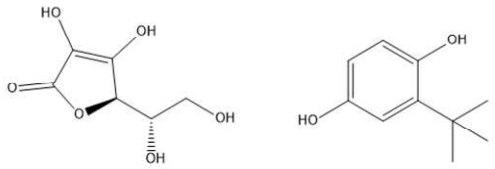


Figure 2. Ascorbic Acid (left) and TBHQ (right)

Results and Discussion

HOMO and LUMO are critical parameters for predicting the most reactive positions in a molecule based on its electron density. HOMO represents the ability to donate electrons (ionization potential), while LUMO indicates the ability to accept electrons (electron affinity). Molecules with higher HOMO energy exhibit a stronger ability to donate electrons. The most active sites for redox reactions in an antioxidant molecule are characterized by high electron density at the HOMO level (Wright et al., 2001). Reactive Oxygen Species (ROS) are electron-deficient species that require electron donation to stabilize their state. A molecule is considered a good antioxidant if it can easily donate electrons to ROS. Therefore, a molecule with the highest HOMO energy has a greater potential to act as an antioxidant.

Table 2. Antioxidant activity as scavenger of ▪ OH and inhibitor of lipid peroxidation by coumarins (Payá et al., 1992)

No	Molecules	k ▪ OH (1/M.s)	% Inhibition of Lipid Peroxidation
1	Coumarin	Inactive	0
2	4-Hydroxy coumarin	Inactive	0.6±0.4
3	7-Hydroxy coumarin	6.1×10^9	3.2±1.1
4	7-Methyl coumarin	4.0×10^9	0.1±0.1
5	7-Methoxy coumarin	7.1×10^9	3.0±1.7

According to the experimental results by Payá et al. (see Table 2), the ▪ OH radical scavenging ability follows the order:

7-Hydroxycoumarin > 4-Hydroxycoumarin > coumarin (Payá et al., 1992). This aligned with the computational results in this study, demonstrating that 7-Hydroxycoumarin had a higher HOMO energy (-6.253 eV) compared to 4-Hydroxycoumarin (-6.509 eV) and coumarin (-6.616 eV). In other words, 7-Hydroxycoumarin could more readily donate electrons to ROS. Additionally, 7-Hydroxycoumarin had a narrower energy gap than 4-Hydroxycoumarin and coumarin. The visualization of HOMO energy and energy gaps is presented in Figure 3. For reference, the energy gap for several antioxidants is as follows: ascorbic acid (3.48 eV) (Nasidi et al., 2022) and quercetin (3.56 eV) (Cai et al., 2014). Furthermore, based on the findings of Payá et al., the ▪OH radical scavenging ability follows the order: 7-Methoxycoumarin > 7-Methylcoumarin > 4-Hydroxycoumarin. This was supported by the computational results in this study, where 7-Methoxycoumarin had a higher HOMO energy (-6.19 eV) compared to 7-Methylcoumarin (-6.437 eV) and 4-Hydroxycoumarin (-6.509 eV).

computational results indicated that the IP values aligned with the experimental findings reported by Payá et al. (1992), with the following order: 7-Hydroxycoumarin (183.57 kcal/mol) < 4-Hydroxycoumarin (190.04 kcal/mol) < coumarin (193.77 kcal/mol). A smaller IP value signified a molecule more readily donated electrons and underwent ionization. However, the BDE values did not correspond to the experimental results: the BDE value of 7-Hydroxycoumarin (82.56 kcal/mol) was higher than that of 4-Hydroxycoumarin (81.75 kcal/mol). This discrepancy suggested that the H-atom transfer via homolytic cleavage of the O-H bond was easier for 4-Hydroxycoumarin than for 7-Hydroxycoumarin, contrary to the experimental findings.

Based on the observation, this study employed HOMO energy, the energy gap, and IP values to identify the antioxidant activity of various coumarin derivatives. BDE values or H-transfer mechanisms were not utilized due to their inconsistency with experimental results. Additionally, determining the transferred H atom became

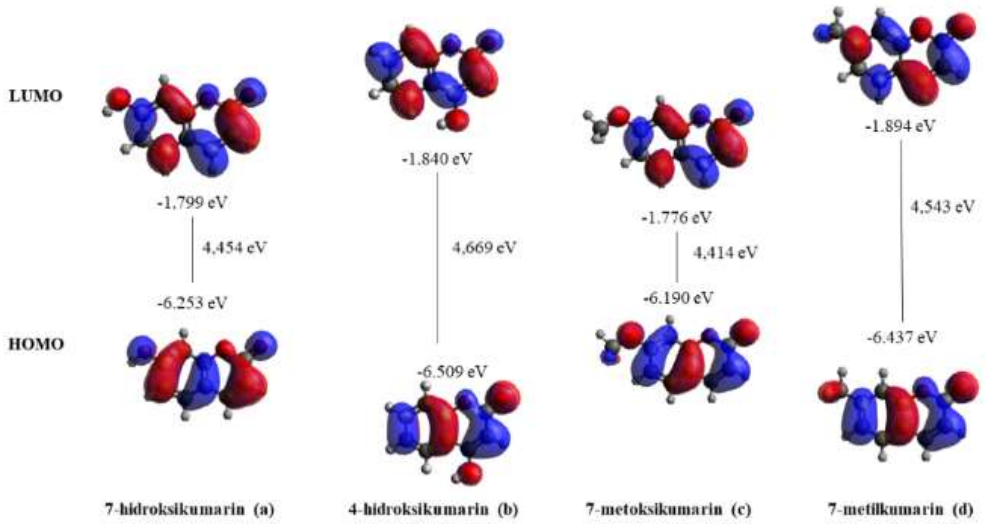


Figure 3. HOMO-LUMO Energy of (a) 7-Hydroxycoumarin, (b) 4-Hydroxycoumarin, (c) 7-Methoxycoumarin, and (d) 7-Methylcoumarin

The antioxidant activity of 7-Hydroxycoumarin, 4-Hydroxycoumarin, and coumarin could further be correlated with their ionization potential (IP) and bond dissociation energy (BDE) values. The

challenging for compounds that were not hydroxycoumarins, such as methoxycoumarins or methylcoumarins. Nevertheless, 7-Methoxycoumarin and 7-Methylcoumarin exhibited better ▪OH scavenging activity than 4-

Hydroxycoumarin (Payá et al., 1992). Computational results consistently explained this phenomenon through IP values, with the following order: 7-Methoxycoumarin (180.21 kcal/mol) < 7-Methylcoumarin (183.57 kcal/mol) < 4-Hydroxycoumarin (190.04 kcal/mol). It should be noted that the IP values were calculated in the gas phase; in solution, these values might vary due to solvent effects. Zhang and Wang (2004) have reported that the average difference between IP values in the gas phase and in solution is approximately ±10 kcal/mol.

In this study, the antioxidant activities of coumarin derivatives were computationally evaluated to predict which derivatives were most likely to be effective antioxidants. In the initial computational experiments, the substituents on the benzene ring of coumarin compounds—namely OH, OCH_3, and CH_3—were varied to observe their effects on IP values and antioxidant activity. The results indicated the following order of IP values: 7-Methoxycoumarin < 7-Hydroxycoumarin < 7-Methylcoumarin, as shown in Table 3. Thus, 7-Methoxycoumarin exhibited the highest antioxidant activity. This finding aligned with the experimental results of Payá et al. (1992), demonstrating that 7-Methoxycoumarin had the highest reaction rate constant with ▪ OH (7.1×10^9 $M^{-1}s^{-1}$), compared to 7-Hydroxycoumarin (6.1×10^9 $M^{-1}s^{-1}$) and 7-Methylcoumarin (4.0×10^9 $M^{-1}s^{-1}$) (Payá et al., 1992).

Antioxidant activity involving electron transfer mechanisms accompanied by protons, or conversely, proton transfer mechanisms accompanied by electrons, is affected by inductive and resonance effects. The inductive effect is related to the electronegativity of substituent groups. Less electronegative groups act as electron-donating groups, increasing the electron density in a molecule, while more electronegative groups are electron-withdrawing, decreasing electron density. Electron-donating groups produce a positive inductive effect (+I), whereas electron- withdrawing groups produce a negative inductive effect (-I). Unlike the inductive effect, which involves electrons in σ bonds, the resonance effect involves the polarization of electrons in π bonds. Electron-donating groups contribute to a positive resonance effect (+R), while electron-withdrawing groups contribute to a negative resonance effect (-R). A molecule with substituted functional groups can exhibit both inductive and resonance effects, but one typically dominates in determining the molecule's properties. The presence of electron-donating groups facilitates electron transfer but may hinder proton transfer. Conversely, electron-withdrawing groups facilitate proton transfer but may hinder electron transfer (Nakayama & Uno, 2024).

The ionization potential (IP) value of 7-Methylcoumarin (187.84 kcal/mol) was lower than that of coumarin (193.78 kcal/mol), indicating that the CH_3 group in coumarin facilitated easier electron transfer. This occurred due to the +I effect of the CH_3 group, an electron-donating group that increased the electron density in coumarin. For the OH and OCH_3 groups, exhibiting both -I and +R effects, the resonance effect on the coumarin molecule dominated over the inductive effect. The lone pair of electrons on the oxygen atom in these groups could resonate with the π electrons of the benzene ring in the coumarin molecule, increasing electron density and making electron transfer easier. This aligned with findings that the IP values of 7-Hydroxycoumarin (183.57 kcal/mol) and 7-Methoxycoumarin (180.21 kcal/mol) were lower than that of coumarin. Although both the OH and OCH_3 groups had -I and +R effects, 7-Methoxycoumarin had a lower IP value than 7-Hydroxycoumarin because the OCH_3 group exhibited a stronger +R effect than the OH group. Experimental results supported this, showing that p-methoxyphenol had a pKa of 10.21. In contrast, p-hydroxyphenol had a pKa of 9.96, indicating that the OCH_3 group made proton transfer more difficult than the OH group (Liptak et al., 2002). In other words, the OCH_3 group acted as a stronger electron-donating group, facilitating easier electron transfer.

Table 3. Comparison of the number and type of substituents on the benzene ring of coumarin compounds

No	Molecules	HOMO (eV)	Gap (eV)	IP (gas) (kcal/mol)
1	Coumarin	-6.616	4.601	193.78
2	4-Hydroxycoumarin	-6.253	4.454	183.57
3	7-Hydroxycoumarin (Umbelliferone)	-6.190	4.414	180.21
4	7-Methoxycoumarin (Herniarin)	-6.437	4.543	187.84
5	7-Formylcoumarin	-6.960	4.195	199.53
6	6,7-Dihydroxycoumarin (Esculetin)	-5.925	4.165	174.90
7	7-Hydroxy-6-Methoxycoumarin (Scopoletin)	-5.855	4.158	171.85
8	6,7-Dimethoxycoumarin (Scoparone)	-5.700	4.050	166.50

The highest electron density in the coumarin molecule was located at the oxygen atom (C=O). According to this study finding, the highest occupied molecular orbital (HOMO) of the coumarin molecule was at the 37th orbital, where the oxygen atom (C=O) had the largest electron density, quantified as 0.270467. This result indicated that this group was the active site for electron transfer in the coumarin molecule. The presence of an OCH_3 group on the benzene ring of coumarin, through its positive resonance effect, increased the electron density in that region, as illustrated in Figure 4. Meanwhile, the negative resonance effect of groups like CHO reduced electron density. This was reflected in the IP values, where 7-Formylcoumarin (199.53 kcal/mol) had a higher IP than coumarin (193.77 kcal/mol), indicating that 7-Formylcoumarin was less likely to donate electrons compared to coumarin.

activity. The results indicated that increasing the number of substituents affected the ease with which coumarin released electrons, as displayed in Table 3. For example, the IP value of 6,7-Dihydroxycoumarin (174.90 kcal/mol) was lower than that of 7-Hydroxycoumarin (183.57 kcal/mol), indicating that adding -OH groups could facilitate easier electron transfer. This condition was due to the stronger +R effect contributed by the two -OH groups. Consistent with previous results, the OCH_3 group exhibited a greater +R effect compared to the OH group. Therefore, the IP values followed the order: 6,7-Dimethoxycoumarin (166.50 kcal/mol) < 7-Hydroxy-6-Methoxycoumarin (171.85 kcal/mol) < 6,7-Dihydroxycoumarin (174.90 kcal/mol). Consequently, in the next computational experiment, derivatives of 6,7-Dimethoxycoumarin (scoparone) were investigated.

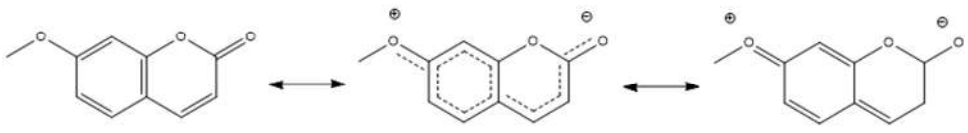


Figure 4. positive resonance effect of the methoxy group on the coumarin molecule (Donovalová et al., 2012)

In the second computational experiment the number of substituents on the benzene ring of coumarin was varied—either one or two substituents—to observe their impact on IP values and antioxidant

Scoparone could be substituted at position 3 using boronic acid reagents ($RB(OH)_2$), catalyzed by $KMnO_4$/AcOH at 80°C for 2 hours (Kumar et al., 2023). The derivatives of scoparone studied were those

substituted at position 3 with CH_3, Br, and CHO groups. In the third computational experiment of this study, the type of substituent was varied to observe its effect on the IP value. The results demonstrated that the IP value of 3-Methylscoparone (162.84 kcal/mol) was lower than that of scoparone (166.50 kcal/mol). This was because the CH_3 group exhibited a +I effect, increasing the molecule's electron density. Conversely, the IP value of 3-Bromoscoparone (166.69 kcal/mol) was slightly higher than that of scoparone (166.50 kcal/mol). The -I effect of the Br group decreased the electron density, making electron release more difficult. Although the Br group also exhibited a +R effect, its resonance was less significant than the benzene ring, owing to the lower abundance of π-electrons in the pyrone ring. Hence, the -I effect of the Br group slightly outweighed the +R effect. The IP value of 3-Formylscoparone (172.85 kcal/mol) was higher than that of scoparone (166.50 kcal/mol), as the CHO group was an electron-withdrawing group with both -I and -R effects. Electron-withdrawing groups like CHO reduced the molecule's electron density, making electron release more challenging. A comparison of the substituent types on the pyrone ring is presented in Table 4.

commonly used as a food additive, particularly in cooking oils, to prevent oxidation

In this study, the toxicity properties and drug scores of coumarin and its derivatives were analyzed using OSIRIS Property Explorer software. A drug score closer to 1.0 indicated a higher potential for the compound to be developed as a drug. The toxicity risk levels were categorized as follows: 1.0 for low risk, 0.8 for moderate risk, and 0.6 for high risk. The results revealed that the compound 3-Methylscoparone had a higher drug score of 0.83 compared to TBHQ (0.55) and ascorbic acid (0.74). Meanwhile, 4-Hydroxycoumarin had a drug score only slightly higher than that of TBHQ, at 0.56. The drug scores and toxicity levels of several coumarin derivatives and antioxidants are presented in Table 6. Other compounds studied exhibited lower drug scores than both TBHQ and ascorbic acid. However, herniarin and scopoletin demonstrated reasonably good drug scores without side effects. In this context, "without side effects" refers to compounds with very low toxicity risk. The toxicity risk levels were determined based on structural fragment similarities between the studied compounds and known toxic compounds. The structural fragments of these toxic compounds were available in the

Table 4. Comparison of substituent types on the pyrone ring of coumarin compounds

No	Molecules	HOMO (eV)	Gap (eV)	IP (gas) (kcal/mol)
1	Scoparone	-5.700	4.050	166.50
2	3-Methylscoparone	-5.584	4.095	162.84
3	3-Bromoscoparone	-5.786	3.908	166.69
4	3-Formylscoparone	-6.041	3.559	172.85

In this study, the ionization potential (IP), HOMO energy, and energy gap of commercial antioxidants such as ascorbic acid and TBHQ were calculated as positive controls, as shown in Table 5. Vitamin C, or ascorbic acid, is a naturally occurring organic compound with antioxidant properties found in both animals and plants. This compound functions to neutralize reactive oxygen species (ROS). On the other hand, TBHQ is a synthetic antioxidant

OSIRIS Property Explorer software database. Nevertheless, further research is necessary to confirm that these compounds are entirely free from side effects.

Table 6. Drug scores and toxicity of several coumarin derivatives and antioxidants

No	Molecules	Drug Score	Toxicity Risk			
			Mutagenic	Tumorigenic	Irritant	Reproductive Effect
1	Coumarin	0.12	0.6	0.6	1.0	0.6
2	7-Hydroxycoumarin (Umbelliferone)	0.29	0.6	1.0	1.0	1.0
3	7-Methoxycoumarin (Herniarin)	0.48	1.0	1.0	1.0	1.0
4	7-Methylcoumarin	0.28	1.0	1.0	0.6	1.0
5	7-Formylcoumarin	0.28	1.0	1.0	0.6	1.0
6	4-Hydroxycoumarin	0.56	1.0	1.0	1.0	1.0
7	6,7-Dihydroxycoumarin (Esculetin)	0.29	1.0	0.6	1.0	1.0
8	7-Hydroxy-6-Methoxycoumarin (Scopoletin)	0.49	1.0	1.0	1.0	1.0
9	6,7-Dimethoxycoumarin (Scoparone)	0.34	1.0	1.0	1.0	0.6
10	3-Methylscoparone	0.83	1.0	1.0	1.0	1.0
11	3-Bromoscoparone	0.26	1.0	1.0	1.0	0.6
12	3-Formylscoparone	0.39	1.0	1.0	0.6	1.0
13	Vitamin C (Ascorbic Acid)	0.74	1.0	1.0	1.0	1.0
14	TBHQ	0.55	1.0	1.0	1.0	1.0

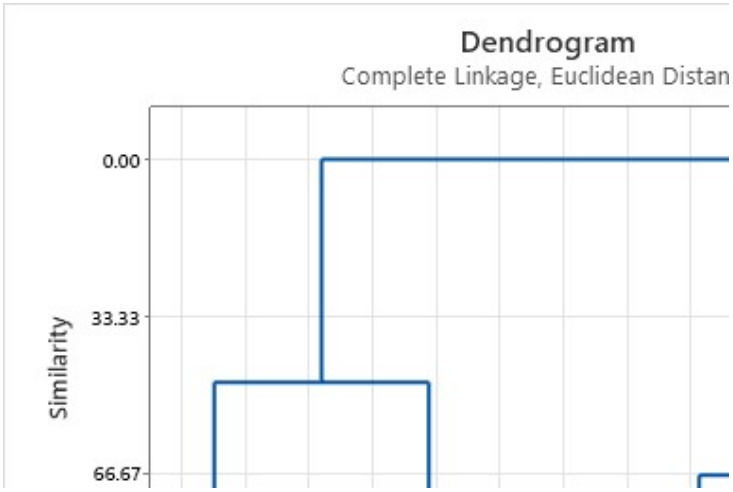


Figure 5. Dendrogram of similarity between commercial and predicted antioxidants

Table 7. Tanimoto coefficient of molecular similarity

No	Molecules	Tanimoto Coefficient	
		Ascorbic Acid	TBHQ
1	Coumarin	0.1250	0.0811
2	7-Hydroxycoumarin (Umbelliferone)	0.1429	0.2647
3	7-Methoxycoumarin (Herniarin)	0.0851	0.1220
4	7-Methylcoumarin	0.0909	0.1316
5	7-Formylcoumarin	0.0870	0.0976
6	4-Hydroxycoumarin	0.1667	0.1892
7	6,7-Dihydroxycoumarin (Esculetin)	0.1250	0.1944
8	7-Hydroxy-6-Methoxycoumarin (Scopoletin)	0.1224	0.1905
9	6,7-Dimethoxycoumarin (Scoparone)	0.0870	0.1250
10	3-Methylscoparone	0.0851	0.0952
11	3-Bromoscoparone	0.0833	0.0930
12	3-Formylscoparone	0.0800	0.0889
13	Vitamin C (Ascorbic Acid)	1.0000	0.0714
14	TBHQ	0.0714	1.0000

Several compounds listed in Table 6 were analyzed for similarity using Hierarchical Clustering Analysis (HCA) based on molecular properties such as E_{HOMO}, EGap, IP, and drug scores. A dendrogram was generated using Minitab software, as displayed in Figure 5. The results indicated that commercial antioxidants, such as ascorbic acid, had a similarity of 96.62% with 7-Hydroxycoumarin. Meanwhile, TBHQ revealed a similarity of 95.72% with scoparone and 3-Bromoscoparone. Although some of these compounds exhibited similarity based on computational data, further research is essential to confirm their potential as antioxidants without side effects.

The compounds listed in Table 6 were analyzed for similarity based on molecular structure (functional groups) using Python software. The Tanimoto Coefficient was calculated, as shown in Table 7. The results indicated that coumarin and its derivatives structurally did not exhibit high similarity with vitamin C or TBHQ. However, vitamin C and TBHQ also did not display significant similarities despite both being antioxidants. Notably, the Tanimoto Coefficient for coumarin and its derivatives was higher than the similarity between TBHQ and vitamin C. This result suggested that the structure of coumarin derivatives was more consistent within their group. Umbelliferone exhibited the highest similarity to both vitamin C and TBHQ among the coumarin derivatives.

Conclusion

The antioxidant activity of coumarin derivatives was affected by their chemical structure, particularly the nature and position of substituent groups. Electron-donating groups with +I or +R effects increased the molecule's electron density, making substituted coumarins more prone to releasing electrons and resulting in a lower ionization potential (IP). In contrast, electron-withdrawing groups with -I or -R effects reduced electron density, making electron release more difficult and leading to a higher IP. Substituents on the benzene ring exerted a more significant effect on antioxidant activity than those on the coumarin molecule's pyrone ring. Therefore, modifications should primarily target the benzene ring when designing synthetic antioxidants based on coumarin. Notably, several compounds examined in this study, such as Umbelliferone, Scoparone, and 3-Bromoscoparone, exhibited antioxidant properties

comparable to those of commercial antioxidants like ascorbic acid and TBHQ.

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