Computational Study of the Influence of Structure on Antioxidant Activity and Drug Score of Coumarin Derivatives

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ABSTRACT

The presence of reactive oxygen species (ROS) in the body must be maintained at low concentrations, excessive ROS and an inability to neutralize them can lead to oxidative stress. Coumarin, a secondary metabolite in plants, is used in pharmacology as an antioxidant agent. This study aims to identify the effects of the type, number, and position of substituents on coumarin derivatives antioxidant activity and drug score using DFT methods. Computational tools, including ORCA software and OSIRIS Property Explorer, were employed. The results indicate that the number and position of electron-donating substituents, such as OCH3, enhance antioxidant activity, while electron-withdrawing substituents, like CHO, decrease it. Additionally, the presence of conjugated double bonds in the pyrone ring causes electron delocalization, complicating electron transfer. The compound 6,7-dimethoxyhydrocoumarin (hydroscoparone) shows potential as a new antioxidant due to its energy gap similar to commercial antioxidants like ascorbic acid and TBHQ, and a drug score of 0.5 with very low toxicity risk. However, further research is needed to confirm that this compound can be used as an effective antioxidant without side effects.

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

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INTRODUCTION

Superoxide radical (▪O_2^-), hydroxyl radical (▪OH), peroxyl radical (▪OOR), alkoxyl radical (▪OR), nitrite oxide (NO▪), 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 needs to be maintained at low concentrations. If ROS levels become excessive and the body is unable to neutralize them, it leads to a condition known as oxidative stress. This condition can trigger various diseases such as atherosclerosis, Alzheimer's disease, diabetes, tumors, and other illnesses. Environmental factors such as UV radiation and pollutants (heavy metals, cigarette smoke, drugs, and pesticides) significantly contribute to increased ROS levels in the body (Pizzino et al., 2017). Therefore, the body requires intake of foods containing antioxidants. Antioxidants are substances that can prevent, slow down, or eliminate oxidative damage to target molecules. Antioxidant compounds can block the oxidation of other substances by directly scavenging ROS or indirectly by inhibiting ROS production in the body (Gulcin, 2020).

Coumarin (1,2-benzopyrone or 2H-1-benzopyran-2-one) represents all compounds that contain a benzene ring fused with a pyrone ring. Coumarin is a secondary metabolite of plants, characterized by its sweet aroma, similar to vanilla. Coumarin and its derivatives have specific biological properties depending on their chemical structure, particularly variations in substitution patterns within their structure. In pharmacology, coumarin is used as an antimicrobial, antioxidant, anti-inflammatory, anti-HIV, anticancer, anticoagulant, antiviral, and anti-tuberculosis agent. In nature, coumarin is found in many plants, the most familiar of which is in the food flavoring cinnamon bark. Despite its numerous health benefits, in excessive doses above 0.1 mg/kg body weight per day, it can cause hepatotoxic effects (Lončar et al., 2020). Coumarin derivatives have been identified as nearly 1300 compounds, primarily as secondary metabolites in plants, fungi, and bacteria (Fylaktakidou et al., 2004). Several coumarin derivatives act as antioxidants because they can interact with ROS. Coumarins substituted with a hydroxyl group on the benzene ring can act as

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better ▪OH radical scavengers compared to coumarins substituted on the pyrone ring, and even more so compared to those that are unsubstituted.

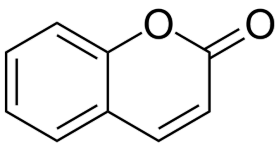


Figure 1. Simple molecular structure of coumarin (Loncar et al., 2020)

The order is 7-hydroxycoumarin > 4-hydroxycoumarin > coumarin. Additionally, coumarins substituted with methyl and methoxy groups on the benzene ring are better ▪OH radical scavengers compared to those substituted with hydroxyl groups on the pyrone ring. The order is 7-methoxycoumarin > 7-hydroxycoumarin > 7-methylcoumarin > 4-hydroxycoumarin. Furthermore, coumarins with two hydroxyl groups on the benzene ring exhibit unique properties. When coumarins are substituted with two hydroxyl groups at the ortho- position (o-dihydroxycoumarin), such as 6,7-dihydroxy-4-methylcoumarin, they can act as pro-oxidants, whereas at the meta- or para- positions, such as 5,7-dihydroxy-4-methylcoumarin, they act as ▪OH scavengers (Payá et al., 1992).

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

The reactivity and antioxidant activity of coumarin derivatives can be determined based on HOMO energy values, energy gaps, O-H BDE, and IP through computational calculations using ORCA software. Experimentally, methods used for 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 include TEAC (Trolox Equivalence Antioxidant Capacity), FRAP (Ferric Ion Reducing Antioxidant Power), DPPH (2,2-Diphenyl-1-picrylhydrazyl Radical Scavenging Assay), and others (Gulcin, 2020). The ABTS (2,2-Azinobis 3-ethylbenzthiazoline-6-sulfonic Acid Radical Scavenging Assay) method is used for both HAT and SET mechanisms.

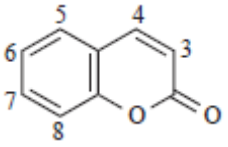
The drug score is a combination of various factors including drug similarity, partition coefficient (cLog P), solubility (Log S), molecular weight, and toxicity risk. The cLog P value of a compound is the logarithm of its partition coefficient between n-octanol and water. This value measures the hydrophilicity of the compound; a higher cLog P indicates lower hydrophilicity and poor absorption. The Log S value represents the logarithm of solubility, which is useful for avoiding poorly soluble compounds. Solubility significantly affects the permeation and distribution of the compound. Additionally, molecular weight influences absorption, with larger molecular weights generally associated with lower absorption and difficulty reaching the target. Drug similarity is indicated by how many fragments of the compound under investigation are commonly found in commercial drugs. Toxicity risk is indicated by how many fragments of the compound are present in mutagenic, tumorigenic, irritant, and reproductive effect compounds (Wulandari et al., 2020). Drug scores can be determined based on physicochemical properties such as log P, log S, molecular weight, drug similarity, and toxicity risk through computational calculations using the OSIRIS Property Explorer software.

Based on the above discussion, the ability of several coumarin derivatives to act as free radical scavengers is important to investigate. Therefore, this secondary metabolite has potential for use as an antioxidant supplement in the future. This study involves a computational analysis of the influence of structure on the antioxidant activity and drug score of coumarin derivatives using ORCA and OSIRIS Property Explorer software. The aim of this study is to identify the effects of the number, type, and position of substituents on the coumarin compounds with regard to their antioxidant activity and drug score.

RESEARCH METHOD

The materials used in this study include 12 coumarin derivative molecular models as shown in Table 1, as well as positive control compounds, namely ascorbic acid (vitamin C) and tert-butylhydroquinone (TBHQ). The equipment used consists of the Avogadro software for molecular visualization, and ORCA and OSIRIS Property Explorer for computational calculations.

Table 1. Coumarin Derivatives Studied



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	3-methylscoparone	CH_3	H	H	OMe	OMe	H
7	3-bromoscoparone	Br	H	H	OMe	OMe	H
8	3-formylscoparone	CHO	H	H	OMe	OMe	H
9	6,7-dihydroxycoumarin (esculetin)	H	H	H	OH	OH	H
10	7-hydroxy-6-methoxycoumarin (scopoletin)	H	H	H	OMe	OH	H
11	6,7-dimethoxycoumarin (scoparone)	H	H	H	OMe	OMe	H
12	6,7-dimethoxyhydrocoumarin	2H	2H	H	OMe	OMe	H

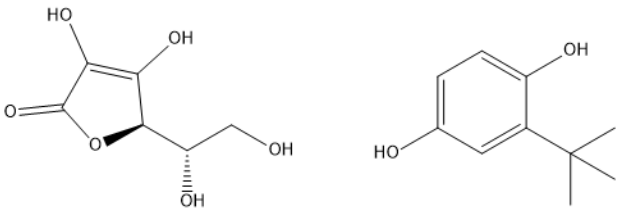


Figure 2. Ascorbic Acid (left) and TBHQ (right)

Molecular Optimization of Coumarin Derivatives

The three-dimensional (3D) structural models of several coumarin derivatives (Table 1) were created using Avogadro software. Subsequently, these coumarin derivatives underwent molecular geometry optimization by minimizing molecular energy to achieve the most stable structural conformation. Computational calculations were performed using the B3LYP method with the def2-SVP basis set through ORCA software. The commands used were !B3LYP D4 def2-SVP Opt Normalprint Printbasis PrintMOs. This process provided data on HOMO energy and energy gap.

Analysis of Antioxidant Activity of Coumarin Derivatives

The optimized molecular structures underwent numerical frequency calculations using the command !B3LYP D4 def2-SVP NumFreq. This provided 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 x 0,9805) - (TE_p + TCE_p x 0,9805) dan O-H BDE = H_r + H_h – H_p.

Toxicity Properties and Drug Score of Coumarin Derivatives

Toxicity and drug score of coumarin derivatives can be determined based on their molecular structure using the OSIRIS Property Explorer software. The obtained data include cLog P, Log S, molecular weight, TPSA, druglikeness, toxicity risks, and drug score.

RESULT AND DISCUSSION

Analysis of Reactivity and Antioxidant Properties of Coumarin Derivatives

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

According to the experimental results by Paya et al. (1992), the radical ▪OH scavenging ability follows the order: 7-hydroxycoumarin > 4-hydroxycoumarin > coumarin (Payá et al., 1992). This is consistent with the computational results in this study, which show that 7-hydroxycoumarin has a higher HOMO energy of -6.253 eV compared to 4-hydroxycoumarin (-6.509 eV) and coumarin (-6.616 eV). In other words, 7-hydroxycoumarin is more readily able to donate electrons to ROS. Additionally, 7-hydroxycoumarin also has a narrower energy gap compared to 4-hydroxycoumarin and coumarin. The visualization of HOMO energy and energy gap is shown in Figure 3. Furthermore, based on the findings of Paya et al. (1992), the ▪OH radical scavenging ability follows the order: 7-methoxycoumarin > 7-methylcoumarin > 4-hydroxycoumarin. This is also supported by the computational results in this study, where 7-methoxycoumarin has a higher HOMO energy of -6.19 eV compared to 7-methylcoumarin (-6.437 eV) and 4-hydroxycoumarin (-6.509 eV).

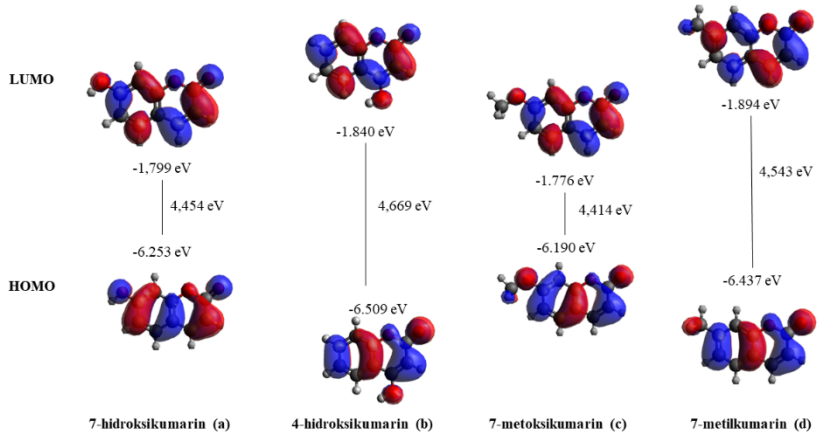


Figure 3. HOMO-LUMO Energy of 7-Hydroxy (a); 4-Hydroxy (b); 7-Methoxy (c); and 7-Methyl (d)

Additionally, the antioxidant activity of 7-hydroxycoumarin, 4-hydroxycoumarin, and coumarin can be correlated with the IP and BDE values. The computational results in this study show that the IP values are consistent with the experimental results of Paya (1992), where the IP values are as follows: 7-hydroxycoumarin (183.57 kcal/mol) < 4-hydroxycoumarin (190.04 kcal/mol) < coumarin (193.77 kcal/mol). A smaller IP value indicates that the molecule is more readily ionizable by donating electrons. However, the BDE values do not align with the experimental results; the BDE value of 7-hydroxycoumarin (82.56 kcal/mol) is higher compared to 4-hydroxycoumarin (81.75 kcal/mol). This suggests that the H-atom transfer through homolytic cleavage of the O-H bond is easier for 4-hydroxycoumarin compared to 7-hydroxycoumarin, contrary to the experimental findings.

Based on the above explanation, this study uses HOMO energy, energy gap, and IP values as the basis for identifying the antioxidant activity of several coumarin derivatives. BDE values or H-transfer mechanisms are not used due to inconsistencies with experimental results. Additionally, determining the transferred H atom is challenging when the compounds are not hydroxycoumarins, such as methoxycoumarin and/or methylcoumarin. Despite this, 7-methoxycoumarin and 7-methylcoumarin are better ▪OH scavengers compared to 4-hydroxycoumarin (Payá et al., 1992). The computational results show that IP values consistently explain this phenomenon, with 7-methoxycoumarin (180.21 kcal/mol) < 7-methylcoumarin (183.57 kcal/mol) < 4-hydroxycoumarin (190.04 kcal/mol). The IP values calculated are in the gas phase; in solution, the values may differ due to the influence of intermolecular forces of the solvent. Zhang & Wang (2004) have noted that the average difference between IP(gas) and IP(solution) is approximately ±10 kcal/mol (Zhang & Wang, 2004).

Through this study, the antioxidant activities of coumarin derivatives were computationally evaluated to predict which coumarin derivatives are most likely to be effective antioxidants. In the initial experiment, the type of substituent on the benzene ring of the coumarin compounds was varied, including OH, OCH_3, and CH_3, to observe its effect on IP values and antioxidant activity. The results indicate that the IP values are as follows: 7-methoxycoumarin < 7-hydroxycoumarin < 7-methylcoumarin, as shown in Table 2. In other words, 7-methoxycoumarin has the highest antioxidant activity. This is consistent with the experiment conducted by Paya et al. (1992), which found that 7-methoxycoumarin has the highest reaction rate constant with ▪OH, at 7.1 x 10^9 $M^{-1}s^{-1}$, while 7-hydroxycoumarin and 7-methylcoumarin have rates of 6.1 x 10^9 $M^{-1}s^{-1}$ and 4.0 x 10^9 $M^{-1}s^{-1}$, respectively (Payá et al., 1992).

Table 2. Comparison of the Number and Type of Substituents on the Benzene Ring of Coumarin Compounds

No	Molekul	HOMO (eV)	Gap (eV)	IP(gas) (kkal/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	6,7-dihydroxycoumarin (esculetin)	-5.925	4.165	174.90
6	7-hydroxy-6-methoxycoumarin (scopoletin)	-5.855	4.158	171.85
7	6,7-dimethoxycoumarin (scoparone)	-5.700	4.050	166.50

Antioxidant activity involving electron transfer mechanisms with accompanying protons, or conversely, proton transfer mechanisms with accompanying electrons, is influenced by inductive and resonance effects. The inductive effect is related to the electronegativity of the substituent groups. Less electronegative groups are electron-donating groups that can increase the electron density in a molecule, while more electronegative groups are electron-withdrawing groups that can decrease electron density. Electron-donating groups result in a positive inductive effect (+I), whereas electron-withdrawing groups result in 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 result in a positive resonance effect (+R), while electron-withdrawing groups result in a negative resonance effect (-R). A molecule with substituted functional groups can exhibit both inductive and resonance effects, but one will typically dominate in influencing the molecule's properties. The presence of electron-donating groups facilitates electron transfer but can hinder proton transfer. Conversely, electron-withdrawing groups facilitate proton transfer but can hinder electron transfer (Nakayama & Uno, 2024).

The IP value of 7-methylcoumarin (187.84 kcal/mol) is lower than that of coumarin (193.78 kcal/mol), indicating that the presence of the CH_3 group in coumarin facilitates easier electron transfer. This is due to the +I effect of the CH_3 group, which is an electron-donating group that can increase the electron density in coumarin. However, for the OH and OCH_3 groups, which have -I and +R effects, the resonance effect on the coumarin molecule is more dominant than the inductive effect. The lone pair of electrons on the oxygen atom in both groups can resonate with the π electrons of the benzene ring in the coumarin molecule, thus increasing the electron density and making electron transfer easier. This is consistent with the findings that the IP values of 7-hydroxycoumarin (183.57 kcal/mol) and 7-methoxycoumarin (180.21 kcal/mol) are lower compared to coumarin. Interestingly, although both the OH and OCH_3 groups have -I and +R effects, 7-methoxycoumarin has a lower IP value than 7-hydroxycoumarin. The OCH_3 group has a stronger +R effect compared to the OH group. This is supported by experimental results showing that p-methoxyphenol has a pKa of 10.21, while p-hydroxyphenol has a pKa of 9.96, indicating that the OCH_3 group makes proton transfer more difficult compared to the OH group (Liptak et al., 2002). In other words, the OCH_3 group is a stronger electron-donating group that facilitates easier electron transfer.

The highest electron density in the coumarin molecule is located at the oxygen atom (C=O). According to the results of this study, the HOMO of the coumarin molecule is located in the 37th orbital, where the highest electron density is at the oxygen atom (C=O), with a value of 0.270467. This indicates that this group is the active region for electron transfer in the coumarin molecule. The presence of the OCH3 group on the benzene ring of coumarin, through its positive resonance effect, leads to an increase in electron density in this region. The mechanism of electron polarization is shown in Figure 4.

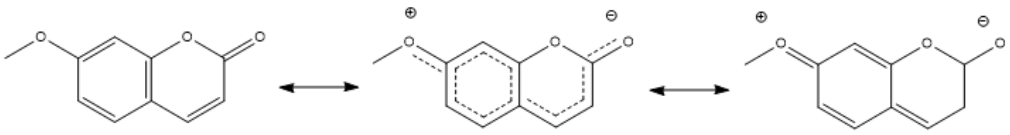


Figure 4. Positive resonance effect of the methoxy group on the coumarin molecule (Donovalová et al., 2012)

In the second experiment of this study, the variable of the number of substituents on the benzene ring of coumarin was varied, with one or two substituents, to observe their impact on IP values and antioxidant activity. The results indicate that increasing the number of substituents affects the ease with which coumarin releases electrons, as shown in Table 2. For example, the IP value of 6,7-dihydroxycoumarin (174.90 kcal/mol) is smaller than that of 7-hydroxycoumarin (183.57 kcal/mol), meaning that adding -OH groups facilitates easier electron transfer. This is due to the stronger +R effect contributed by the two groups. Consistent with previous results, the OCH_3 group has a greater +R effect compared to the OH group. Therefore, the IP values are in the order: 6,7-dimethoxycoumarin (166.50 kcal/mol) < 7-hydroxy-6-methoxycoumarin (171.85 kcal/mol) < 6,7-dihydroxycoumarin (174.90 kcal/mol). Hence, in the next experiment, derivatives of 6,7-dimethoxycoumarin (scoparone) are to be investigated.

Scoparone can 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 are those substituted at position 3 with CH_3, Br, and CHO. In the third experiment of this study, the type of substituent was varied to observe its effect on the IP value. The results show that the IP value of 3-methylscoparone (162.84 kcal/mol) is lower than that of scoparone (166.50

kcal/mol). This is because the CH_3 group has a +I effect that increases the electron density of the molecule. Conversely, the IP value of 3-bromoscoparone (166.69 kcal/mol) is slightly higher than that of scoparone (166.50 kcal/mol). The -I effect of the Br group decreases the electron density, making electron release more difficult. Although the Br group has a +R effect, its resonance is not as significant as that of the benzene ring due to the lower abundance of π-electrons in the pyrone ring. Hence, the -I effect of the Br group is slightly more dominant than the +R effect. The IP value of 3-formylscoparone (172.85 kcal/mol) is greater than that of scoparone (166.50 kcal/mol), as the CHO group is an electron-withdrawing group with both -I and -R effects. Electron-withdrawing groups like CHO reduce the electron density of the molecule, making electron release more challenging. The comparison of substituent types on the pyrone ring is shown in Table 3.

Table 3. Comparison of Substituent Types on the Pyrone Ring of Coumarin Compounds

No	Molecules	HOMO (eV)	Gap (eV)	IP(gas) (kkal/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 addition to the substituent group factors, the presence of double bonds in the scoparone structure affects its ease of electron release. The compound hydroscoparone has a lower IP value (162.08 kcal/mol) compared to scoparone (166.50 kcal/mol), indicating that hydroscoparone releases electrons more easily. In the case of polyhydroxy compounds, catechin has the same number of -OH groups as quercetin but exhibits lower antioxidant activity. This is because the catechin structure lacks conjugated C-C double bonds with -C=O, which are present in quercetin (Gulcin, 2020). However, in the case of scoparone, which is not polyhydroxy, scoparone involves electron transfer mechanisms; conjugated double bonds result in broader electron delocalization, making the delocalized electrons more difficult to release.

In this study, the IP value, HOMO energy, and energy gap of commercial antioxidants such as ascorbic acid and TBHQ were also calculated as positive controls, as shown in Table 4. Compared to the kumarin derivatives studied, only hydroscoparone has an energy gap similar to that of the commercial antioxidants. Therefore, hydroscoparone has potential as a semi-synthetic antioxidant, where scoparone, which is naturally occurring, is modified by reduction.

Table 4. Comparison of Predictive and Commercial Antioxidants

No	Molecules	HOMO (eV)	Gap (eV)	IP(gas) (kkal/mol)
1	Hydroscoparone	-5.554	5.263	162.08
2	Vitamin C (ascorbic acid)	-6.059	5.569	183.33
3	TBHQ	-5.434	5.296	166.11

Toxicity and Drug Score Analysis of Coumarin Derivatives

In this study, the toxicity and drug score properties of coumarin and its derivatives were analyzed using the OSIRIS Property Explorer software. A drug score approaching 1.0 indicates that a compound has a higher potential to be developed into a drug. Toxicity risk is categorized as low, moderate, or high, with values of 1.0, 0.8, and 0.6, respectively. The results show that 3-methylscoparone has a higher drug score of 0.83 compared to TBHQ (0.55) and ascorbic acid (0.74). Meanwhile, 4-hydroxycoumarin has a drug score of 0.56, which is only higher than TBHQ. The drug scores and toxicity results for several coumarin derivatives and antioxidants are shown in Table 5. Other compounds studied had lower drug scores than TBHQ and ascorbic acid. However, herniarin, scopoletin, and hydroscoparone exhibited fairly good drug scores with very low side effect risks. In this study, compounds without side effects are defined as having very low toxicity risk, based on the analysis of structural fragment similarities between the tested compounds and toxic compounds available in the OSIRIS Property Explorer database. Nevertheless, further research is required to confirm that these compounds are truly free of side effects.

Table 5. Drug Scores and Toxicity of Several Coumarin Derivatives and Antioxidants

No	Molecules	Drug Score	Toxicity Risk			
			Mutagenic	Tumorigenic	Irritant	Reproduction 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	4-hydroxycoumarin	0,56	1,0	1,0	1,0	1,0
6	6,7-dihydroxycoumarin (esculetin)	0,29	1,0	0,6	1,0	1,0
7	7-hydroxy-6-methoxycoumarin (scopoletin)	0,49	1,0	1,0	1,0	1,0
8	6,7-dimethoxycoumarin (scoparone)	0,34	1,0	1,0	1,0	0,6
9	3-methylscoparone	0,83	1,0	1,0	1,0	1,0
10	3-bromoscoparone	0,26	1,0	1,0	1,0	0,6
11	3-formylscoparone	0,39	1,0	1,0	0,6	1,0
12	Hydroscoparone	0,50	1,0	1,0	1,0	1,0
13	Vitamin C (askorbic acid)	0,74	1,0	1,0	1,0	1,0
14	TBHQ	0,55	1,0	1,0	1,0	1,0

CONCLUSION

The antioxidant activity of coumarin derivatives is influenced by their chemical structure, particularly the presence of substituent groups and double bonds. Electron-donating groups with +I or +R effects can increase electron density, making coumarins substituted with these groups more likely to release electrons, resulting in lower IP values. Conversely, electron-withdrawing groups with -I or -R effects reduce electron density, making coumarins with these substitutions harder to release electrons, reflected in higher IP values. Additionally, the presence of conjugated double bonds affects the ability of coumarins to release electrons; extensive electron delocalization makes them more stable and harder to release electrons. The coumarin derivative 6,7-dimethoxyhydrocoumarin shows potential as a new antioxidant. It has good antioxidant activity with a low IP value (162.08 kcal/mol) and a similar energy gap to ascorbic acid and TBHQ. Furthermore, 6,7-dimethoxyhydrocoumarin has a favorable drug score (0.50) with no side effects, indicating a very low risk of toxicity.

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