

Investigation of the correlation between skin permeation and global reactivity descriptors in phenolic antioxidants: a comparative DFT and ADMET study

B. Kemanci¹, S. Kurumoglu^{1*}, B. Gurkan²

¹Namik Kemal University, Department of Chemistry, Tekirdag, Turkey

²Gebze Technical University, Department of Physics, Gebze, Turkey

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In the present work the relationship between the skin permeation potential and global reactivity descriptors of four structurally different phenolic compounds, namely ethyl guaiacol, carvacrol acetate, caffeic acid and syringic acid, is explored. Molecular geometries were optimized at the B3LYP/6-311G(d,p) level of density functional theory (DFT). The global reactivity descriptors such as chemical hardness, softness and electrophilicity index were obtained from the frontier molecular orbitals (FMO). The percutaneous permeability coefficients, pharmacokinetic parameters and toxicological profiles were predicted through SwissADME and ProTox-3.0 computational platforms. Marked difference in skin permeability was observed for the alkylated/esterified derivatives as compared to the carboxylic acid analogues. Carvacrol acetate and ethyl guaiacol exhibited higher permeability, whereas caffeic and syringic acids exhibited poor barrier penetration. DFT analysis revealed low chemical hardness and less dipole moments as important electronic factors for diffusion through lipophilic *stratum corneum*. All compounds were predicted to be in Toxicity Class 4 or 5, which confirms their safety for topical applications. Results demonstrate that skin permeability is not only determined by lipophilicity, but also by intrinsic electronic 'softness'. This "Quantum-Permeability" concept provides a predictive approach for the rational design of bioactive molecules for cosmeceutical and transdermal drug delivery systems. The study also shows the utility of DFT with ADMET analysis for the evaluation of their pharmacological potential.

Keywords: ADMET, skin permeation, antioxidants, DFT, electronic reactivity, quantitative surface descriptors

INTRODUCTION

Herbal-derived antimicrobial chemicals (phytochemicals) are divided into three main groups; phenolic compounds, terpenes and alkaloids. These compounds have beneficial antioxidant, antibacterial, and antifungal activities and, when combined with antibiotics, can act as effective resistance-altering agents [1]. Phenolic compounds with antioxidant activity are one of the main substances formed as a result of secondary metabolism of plants [2]. Polyphenols, an important subgroup within phytochemicals, are structurally characterized by their inclusion of one or more phenolic units and are among the most abundant antioxidants in the human diet [3]. Polyphenols have been proposed as one of the most effective functional components with anti-aging properties due to their anti-inflammatory effects, their capacity to neutralize reactive oxygen species (ROS), absorb UV radiation and interact with dermal enzymes involved in connective tissue reconstruction [4]. Naturally occurring antioxidants offer remarkable medical applications in wound healing. But the encapsulation of these phytochemical components

their natural properties such as low molecular weight, poor water solubility and inadequate skin permeability, has always been challenging [5]. For example, syringic acid (SA) is a phenolic acid found in abundance and is derived from olives, spices, grapes, dates and other plants. SA has been proven to have biological effects in a variety of diseases due to its anti-inflammatory, antioxidant and antitumor properties [6]. In one study, a high SA% ratio was observed in different skin layers with limonene-based SA-NE and did not cause dermal irritation. A preclinical study also showed that limonene-based SA-NE was effective in alleviating psoriasis-like skin lesions and against psoriasis caused by imiquimod in rats [7].

Caffeic acid (CA), its protective mechanism, includes direct free radical cleansing and inhibition of nuclear factor kappa-B (NF- κ B)-driven pro-inflammatory pathways; this helps to collectively protect skin cells from UV-induced oxidative stress and MMP-mediated ECM degradation [8]. The human skin can be affected by a wide range of ailments ranging from inflammatory diseases to skin cancer, and no effective treatment has been found for many of them. In particular, some studies have

* To whom all correspondence should be sent:
E-mail: skurumoglu@nku.edu.tr

shown the potential of CA in the treatment of inflammatory pathologies of the skin, such as psoriasis. Moreover, thanks to its antioxidative power, CA can photocorroctect against DNA damage, protecting the skin from aging and preventing melanoma [9]. Similarly, ferulic acid is a powerful antioxidant with scientifically proven skin care effects. However, the instability of this active ingredient in skin care products has restricted its wide use in the beauty and skin care industries. The average particle size of ferulic acid-laden nanocapsules is optimized at <300 nm [10]. Caffeic acid is also a powerful antioxidant molecule that is difficult to apply through the skin due to its low solubility and little stability. Franz cell results showed that caffeic acid diffusion from ethosomes was 18 times slower than solid lipid nanoparticles [11]. Dermal absorption is defined as the transport of substances from the outer surface of the skin into the skin and into the circulatory system. This process is divided into penetration (introduction to a specific layer), permeability (penetration from one layer to another) and resorption (intake to the vascular system) [12]. Topical and transdermal drug administration is an effective, safe and preferred way of administering drugs. Therefore, skin permeability is one of the critical parameters to consider in the process of drug discovery and development. Various *in vitro*, *in vivo* and *ex vivo* test systems have been developed to assess drug retention and skin permeability in the skin layers [13]. The benefits of transdermal delivery of active ingredients include a comparatively large absorption surface area and non-invasiveness. The lipophilicity and molecular size of these compounds have a major impact on the permeability of the active ingredient. Compounds having molecular weight less than 600 may be able to get through the skin's lipophilic barrier [14].

Fatty acid vesicles (FAVs) have lately gained interest as a substitute for conventional delivery methods including liposomes and synthetic polymers. Since FAVs are composed of fatty acids (such oleic acid) and non-ionic stabilizers rather than the phospholipids and cholesterol found in liposomes, they have clear advantages for cutaneous distribution. Fatty acid intermolecular hydrogen bonds and hydrophobic interactions are primarily responsible for their stability, which may provide formulation advantages [15]. Since caffeic acid is characterized by its antioxidant potential but also has high instability, its encapsulation appears to be an interesting strategy. Etosomes are produced by adding water to the solution of phosphatidylcholine ethanol under magnetic mixing. Ethanol also increases the passage of drugs through the skin from

topical formulations. Although it is well known that ethanol penetrates the skin and increases the permeability of both polar and non-polar molecules, the mechanism to increase permeability is not fully explained [16]. One of the more straightforward and all-encompassing methods for transdermal drug delivery (TDD) is the use of chemical penetration enhancers (CPEs), which are preferred in topically administered formulations. These are compounds that interact with intracellular lipids or proteins in the *stratum corneum* (SC) (lipid-protein cleavage theory) or facilitate the drug's percutaneous penetration by rapidly and reversibly boosting the drug's solubility in SC lipids [17].

In *in vitro* permeability studies, vertical Franz diffusion cells are often used to assess the permeability of drugs through the skin or other biologically relevant membranes [18]. Diffusion cell is a simple test that can reliably measure *in vitro* and *ex vivo* drug release from topical preparations such as creams, ointments, liposome formulations and gels [19]. In recent years, computational methods have emerged as powerful tools to explain the hidden mechanisms of skin diseases and advance discoveries concerning current treatments. Overall, the integration of computational chemistry into dermocosmetic research has tremendous potential to accelerate the discovery and development of innovative treatments to improve skin health and address dermatological problems [20].

One of the most applicable and versatile of existing theories in its field is the density functional theory (DFT) which provides an understanding of chemical selectivity through the study of properties of a compound. This method facilitates the explanation of the reactivity of simple and complex systems without a detailed explanation of the reaction pathway [21]. The chemical reactivity of a molecule has been defined through various concepts, such as electronegativity, chemical hardness and softness along with the principle of equalization, and the hard-soft acid-base principle [22]. For example, the free radical scavenging activity of a phenolic antioxidant *via* the HAT reaction can be assessed by measuring the bond dissociation enthalpy (BDE) associated with the homolytic breakage of the O-H bond to form stable phenolic radicals [23]. Propolis contains a naturally occurring phenolic chemical molecule called caffeic acid phenethyl ester (CAPE). By blocking the free radicals of DPPH, peroxide, carboxyl, and hydroxide, CAPE's antioxidant activity is determined. The B3LYP/6-31+G* technique is used to calculate CAPE's performance on free radicals. Caffeic acid phenethyl ester

(CAPE) may have a potent antioxidant impact on the aforementioned radicals, according to the data [24].

Estimating the skin permeability of chemicals is very time consuming and expensive. There are also many ethical challenges associated with human and animal testing for the assessment of skin permeability. Experimental evaluation of ADMET-related traits may be a time-consuming and costly process that requires extensive animal experiments at the early stage of drug discovery [25]. Quantitative structure-activity/toxicity relation (QSAR/QSTR) models can be used to estimate the physicochemical properties of compounds, even for undiagnosed compounds [26].

The main originality of this study; it gives a new perspective to the literature by linking the skin permeability potential not only through classical physicochemical descriptors (logP, TPSA) but with quantum mechanical based global reactivity parameters. While percutaneous transition is usually analyzed by empirical methods, the electronic structure of the molecules by DFT calculations performed at B3LYP/6-311G(d,p) level in this research; chemical hardness, softness and electrophilicity index were examined in depth through dynamic indicators. In particular, the correlation of low dipole moment and the decisive role of reduced chemical hardness in overcoming the lipophilic stratum corneum barrier by classical ADMET parameters provides a more precise and predictive set of criteria for the design of the cosmetological and transdermal drug. By considering both passive diffusion and the possibility of electronic interaction with the molecule's biological environment, this "Quantum-Passioned" approach develops a novel evaluation framework for the logical design of upcoming bioactive compounds.

Materials and methods

Gaussian 09W software with the DFT/B3LYP approach and the 6-311++G(d,p) basis set was used to optimize molecules [27]. The basic dyes used to compute quantum chemical characteristics have had their molecular structures, optimized structures, and HOMO and LUMO orbitals characterized. The HOMO–LUMO energy gap values, including global softness (η), global softness (S), electronic chemical potential (μ), electrophilic index (Ψ), electronegativity (χ), ionization energy (IE), and electron affinity (EA), were roughly calculated using the following equations in terms of HOMO and LUMO orbital energies after the frontier molecular orbital (FMO) was used to estimate the E_{homo} (energy of the highest occupied molecular orbital) and E_{lumo}

(energy of the lowest unoccupied molecular orbital [28].

To evaluate the biological correlation of these electronic parameters, pharmacokinetic profiles and skin permeability coefficients (logKp) were predicted using the SwissADME platform (<https://www.swissadme.ch/index.php>).

Toxicological safety profiles, including acute oral toxicity classes (Class 1-6) and organ toxicity parameters, were determined *via* the ProTox-3.0 computational database (<https://tox.charite.de/protox3/>). This integrated approach elucidates the relationship between molecular reactivity and percutaneous absorption potential on a quantum mechanical basis. following equations in terms of HOMO and LUMO orbital energies.

Quantitative surface descriptors, including the total surface variance (σ_{tot}^2) and molecular polarity index (MPI), were calculated using the Multiwfn software package (version 2026.3.27) [29-30] to evaluate the distribution and variability of the electrostatic potential on the molecular surface. These parameters were determined according to the quantitative analysis of molecular surfaces as described by Bulat *et al.* [31] and the fundamental roles of electrostatic potential established by Politzer and Murray [32].

Analysis was carried out on the 0.001 a.u. isodensity surface as defined by the van der Waals surface. The three-dimensional visualization of the ESP maps and surface projections were generated using UCSF ChimeraX (version 1.11.1) [33].

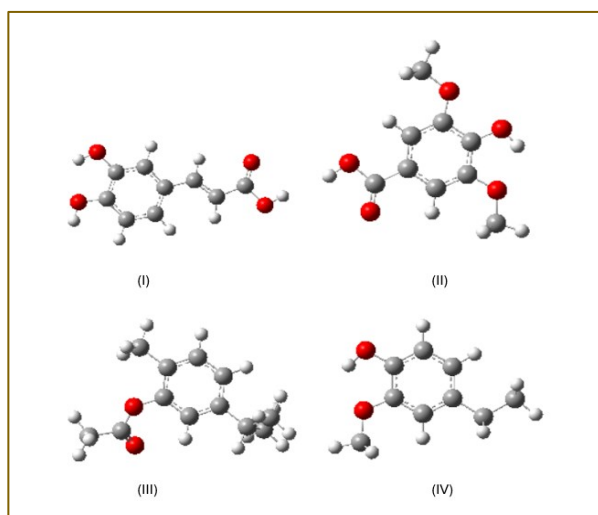


Figure 1. Optimized structures of (i) caffeic acid; (ii) syringic acid; (iii) carvacryl acetate; (iv) ethylguaiaicol (grey, C; white, H; red, O)

RESULTS AND DISCUSSION

The distribution of electrostatic potential on the surface of a molecule has a direct effect on the

electrostatic resistance that is met during passive transport. Caffeic acid has the highest total surface variance ($\sigma_{tot}^2 = 303.12 \text{ kcal}^2/\text{mol}^2$) and the highest molecular polarity index (MPI = 13.63 kcal/mol) of all the compounds we looked at. These quantitative results strongly support the strong charge polarization seen in Figure 2. High variance and MPI values indicate substantial interaction with the polar components of the skin's lipid matrix, leading to an electrostatic retention effect that obstructs efficient diffusion.

Conversely, ethylguaiacol and carvacryl acetate have the lowest values of variance on the surface (102.38 and 112.52, respectively).

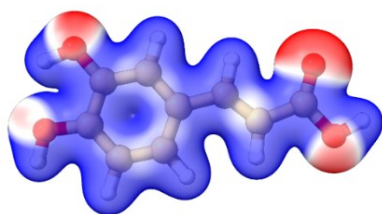


Figure 2. ESP map of caffeic acid projected onto their van der Waals (0.001 a.u. isodensity) surface

This structural feature appears as large electrostatic neutrality regions (white domains) in Figures 3 and 4. Particularly carvacryl acetate has the maximum nonpolar surface area (%73.15) and therefore is determined as the most compatible derivative for rapid transportation through lipophilic extracellular pathways.

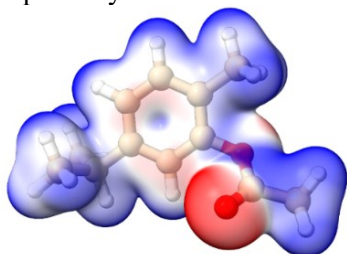


Figure 3. ESP map of carvacryl acetate projected onto their van der Waals (0.001 a.u. isodensity) surface

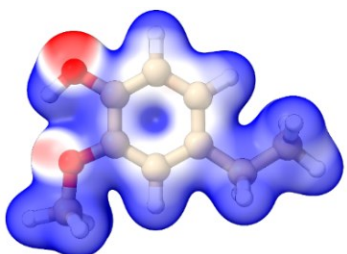


Figure 4. ESP map of ethylguaiacol projected onto their van der Waals (0.001 a.u. isodensity) surface

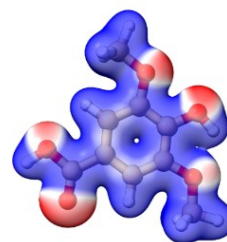


Figure 5. ESP map of syringic acid projected onto their van der Waals (0.001 a.u. isodensity) surface

The values of E_{HOMO} , E_{LUMO} and energy gap (ΔE) of the frontier molecular orbitals of the target compounds are presented in Figure 6. The E_{HOMO} levels range from -6.21 eV to -5.38 eV, with the higher position of ethylguaiacol indicating its greater ability to donate electrons. The calculated energy gaps also show a clear trend in chemical reactivity and kinetic stability, increasing from caffeic acid (4.19 eV) to syringic acid (4.70 eV), ethylguaiacol (5.69 eV) and finally carvacryl acetate (6.02 eV). These observations confirm the fact that the narrow HOMO-LUMO gap makes caffeic acid the most reactive species whereas the wider gap of carvacryl acetate indicates its better structural stability.

Global reactivity parameters were calculated using frontier molecular orbital energies according to the Koopmans' theorem. The chemical potential (μ) is the arithmetic mean of the energies of HOMO and LUMO, while the global hardness (η) is obtained by dividing the HOMO-LUMO energy difference by two. Using these two parameters, the value of the electrophilicity index (ψ) and that of global softness (S) were obtained. Additionally, some other electronic parameters such as electronegativity (χ), ionization energy (IE) and electron affinity (EA) were calculated using the frontier orbital energies.

The equations used in these calculations are stated as follows:

$$\mu = \frac{E_{\{HOMO\}} + E_{\{LUMO\}}}{2} \quad (1)$$

$$\eta = \frac{E_{\{HOMO\}} - E_{\{LUMO\}}}{2} \quad (2)$$

$$\psi = \frac{\mu^2}{2\eta} \quad (3)$$

$$S = \frac{1}{2\eta} \quad (4)$$

$$\chi = -\frac{E_{\{HOMO\}} + E_{\{LUMO\}}}{2} = -\mu \quad (5)$$

$$IE = -E_{\{HOMO\}} \quad (6)$$

$$EA = -E_{\{LUMO\}} \quad (7)$$

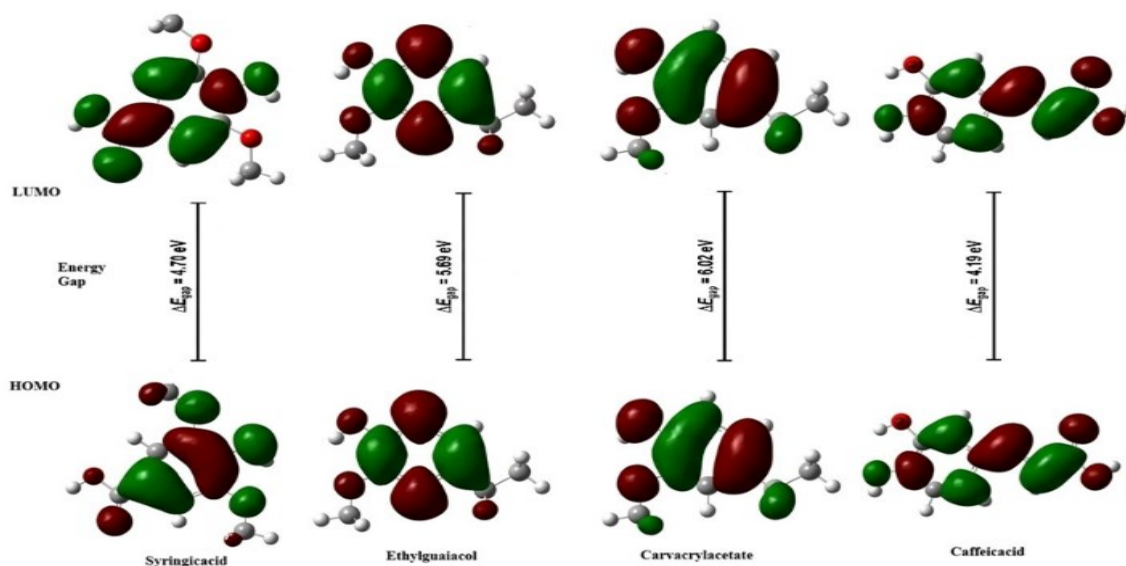


Figure 6. HOMO, LUMO and energy gap of optimized molecules

Table 1. Global reactivity descriptors of optimized molecules

Parameter (eV)	Caffeic acid	Syringic acid	Carvacryl acetate	Ethyl guaiacol
E_{HOMO}	-5.82	-5.67	-6.21	-5.38
E_{LUMO}	-1.63	-0.97	-0.19	+0.31
Energy gap	4.19	4.70	6.02	5.69
Electro-negativity (χ)	3.73	3.32	3.20	2.53
Global hardness (η)	2.10	2.35	3.01	2.84
Global softness (s)	0.48	0.43	0.33	0.35
Global electro-philicity index (Ψ)	3.31	2.34	1.69	1.13

The calculated global reactivity descriptors of the optimized molecules are shown in Table 1. Electronic descriptors displayed carvacryl acetate has the highest energy gap ($E_{\text{gap}} = 6.02$ eV) and the highest Chemical Hardness ($\eta = 3.01$ eV) indicating higher chemical stability. Ethylguaiacol also has the smallest electrophilicity index ($\omega = 1.13$ eV) in the group. The low values of both ω and variance indicate a very low degree of non-specific interactions with the skin matrix, which makes possible passive permeability. Syringic Acid has an intermediate profile as suggested by the moderate variance (165.63) and MPI (12.85) values, which are consistent with the surface properties shown in Figure 5.

Table 2. Skin permeability of optimized molecules

Molecule	Log Kp cm/s	Consensus log Po/w	TPSA Å ²
Caffeic acid	-6.58	0.93	29.46
Syringic acid	-6.77	0.99	26.30
Carvacrol acetate	-5.37	3.02	75.99
Ethyl guaiacol	-5.81	2.02	77.76

The physicochemical parameters relevant to the absorption and permeability profiles of the target compounds are summarized in Table 2. The consensus lipophilicity (log Po/w) ranged from 0.93 to 3.02 with the most lipophilic species being carvacrol acetate (3.02) followed closely by ethyl guaiacol (2.02). The lipophilic behavior observed is also related to the skin permeability, where carvacrol acetate and ethyl guaiacol showed a higher diffusion capacity, with log Kp values of -5.37 and -5.81 cm/s, respectively. In contrast, the more hydrophilic nature of caffeic acid (0.93) and syringic acid (0.99) resulted in a notable decrease in their permeability coefficients (-6.58 cm/s and -6.77 cm/s). Additionally, the topological polar surface area (TPSA) values provided crucial insights into the molecular polarity, positioning ethyl guaiacol (77.76 Å²) and carvacrol acetate (75.99 Å²) as the structures with the most favorable surface properties among the evaluated group.

Table 3. Toxicology values of optimized molecules using SwissADME and Protox-3.0

Molecule	Rat acute toxicity (LD ₅₀ - mol/kg)	Max. tolerated dose (log mg/kg/day)	Skin sensitization
Caffeic acid	1.78	0.27	low
Syringic acid	1.95	1.75	low
Carvacrol acetate	1.89	1.01	low
Ethyl-guaiacol	1.99	0.88	low

The in silico toxicity endpoints evaluated for the studied compounds are compiled in Table 3. The acute toxicity in rats, quantified via LD₅₀ values, followed the upward trend of caffeic acid (1.78 mol/kg) < carvacrol acetate (1.89 mol/kg) < syringic acid (1.95 mol/kg) < ethyl guaiacol (1.99 mol/kg). For the maximum tolerated dose (MTD), the values ranged significantly from 0.27 to 1.75 log mg/kg/day, where syringic acid emerged as the most well-tolerated structure (1.75 log mg/kg/day) and caffeic acid marked the lowest threshold (0.27 log mg/kg/day). Crucially, none of the molecules exhibited high dermatological risk, as all compounds displayed a low potential for skin sensitization. These toxicity indices collectively suggest that while dosage adjustments must consider the lower MTD of caffeic acid, the overall series maintains a promising safety profile.

CONCLUSION

This study investigated the passive diffusion mechanisms of selected phenolic compounds across the skin barrier using quantum chemical descriptors and quantitative electrostatic potential (ESP) surface analysis. The results underscore the critical influence of molecular surface electrostatic properties on permeation rates. Specifically, caffeic acid, characterized by high electrophilicity (ω) and total surface variance, exhibits substantial electrostatic resistance within the skin matrix. In contrast, carvacryl acetate and ethylguaiacol display electrostatically neutral profiles, indicated by low variance and high percentages of nonpolar surface area (73.15% and 59.76%, respectively), which facilitate their diffusion through lipophilic pathways. Structural modifications such as acetylation, exemplified by carvacryl acetate, were found to enhance skin barrier compatibility by increasing chemical hardness and reducing molecular polarity (MPI). Overall, total surface variance and the percentage of nonpolar surface area are proposed as

effective predictors of the skin absorption potential of phenolic derivatives.

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