Research paper **P 28**

COMPARATIVE *IN SILICO* ASSESSMENT OF DRUG-LIKENESS AND ANTIOXIDANT POTENTIAL OF SELECTED DIETARY PHENOLIC ACIDS

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ABSTRACT

In the present study, five representative dietary phenolic acids, namely p-coumaric acid, vanillic acid, caffeic acid, gallic acid, and chlorogenic acid, were comparatively evaluated using an *in silico* descriptor-based approach. Molecular weight (MW), hydrogen-bond donors (HBD), hydrogen-bond acceptors (HBA), lipophilicity (LogP), topological polar surface area (TPSA), rotatable bonds, and Lipinski Rule-of-Five compliance were analyzed to assess drug-likeness and predicted membrane permeability. Among the investigated compounds, caffeic acid provided the most balanced combination of antioxidant activity and physicochemical properties associated with oral absorption.

INTRODUCTION

Phenolic acids constitute one of the largest classes of naturally occurring phytochemicals and are widely distributed throughout fruits, vegetables, cereals, coffee, tea, medicinal plants, and numerous functional foods. These compounds contribute significantly to the antioxidant capacity of plant-derived products and have been associated with various beneficial biological effects. The *in vivo* effectiveness of phenolic acids depends not only on intrinsic chemical reactivity but also on pharmacokinetic behavior. [1]

Drug-likeness represents a conceptual framework used to assess whether a molecule possesses physicochemical characteristics commonly associated with successful orally active drugs. Among the available approaches, Lipinski's Rule of Five remains one of the most widely applied guidelines in medicinal chemistry. Phenolic acids represent an excellent model system for investigating the relationship between antioxidant activity and drug-likeness. [2]

The objective of the present study was to perform a comparative *in silico* assessment of five representative dietary phenolic acids, and to examine the relationship between antioxidant potential and drug-likeness.

EXPERIMENTAL

The molecular descriptors evaluated were molecular weight, hydrogen-bond donor count, hydrogen-bond acceptor count, octanol-water partition coefficient, topological polar surface area, and number of rotatable bonds. Drug-likeness was assessed according to Lipinski's Rule of Five. The following criteria were applied: MW ≤ 500 Da, HBD ≤5, HBA ≤10, and LogP ≤5. The number of violations for each compound was determined and interpreted as an indicator of predicted oral drug-likeness. We evaluated relative antioxidant potential based on established structure-activity principles for phenolic compounds. Particular attention was given to the number of phenolic hydroxyl groups, presence of catechol motifs, methoxy substitution, and expected stabilization of phenoxyl radicals following hydrogen or electron donation. [3]

RESULTS AND DISCUSSION

The investigated compounds exhibited substantial differences in molecular size, polarity, and hydrogen-bonding capacity despite sharing common aromatic acid scaffolds. Table 1 summarizes the descriptor values used for comparative analysis. Among the investigated compounds, chlorogenic acid displayed the highest molecular weight and TPSA, indicating substantially greater polarity than the remaining phenolic acids. In contrast, p-coumaric acid exhibited the lowest TPSA and the highest LogP value, suggesting superior predicted passive membrane permeability. Vanillic acid also showed a favorable descriptor profile, reflecting the permeability-supporting effect of methoxy substitution.

Table 1. Physicochemical descriptors and Lipinski parameters of selected phenolic acids.

Compound	MW (Da)	HBD	HBA	LogP	TPSA (A2)	Rotatable bonds	Violations
p-Coumaric acid	164.16	2	2	1.49	57.53	2	0
Vanillic acid	168.15	2	3	1.10	66.76	2	0
Caffeic acid	180.16	3	3	1.20	77.76	2	0
Gallic acid	170.12	4	4	0.50	97.99	1	0
Chlorogenic acid	354.31	6	8	-0.79	164.75	4	1

All compounds except chlorogenic acid fully satisfied Lipinski's criteria. Chlorogenic acid exhibited one violation due to the presence of six hydrogen-bond donor groups. These results suggest that p-coumaric acid, vanillic acid, caffeic acid, and gallic acid occupy physicochemical space generally associated with favorable oral drug-likeness. In contrast, chlorogenic acid may experience reduced passive membrane transport due to its high polarity and hydrogen-bonding capacity.

The antioxidant activity of phenolic acids is strongly influenced by hydroxylation patterns. Gallic acid contains three phenolic hydroxyl groups and therefore exhibits extensive radical stabilization through resonance mechanisms. Caffeic acid contains a catechol moiety that provides efficient electron delocalization following hydrogen donation. Chlorogenic acid retains the antioxidant characteristics of caffeic acid while introducing additional hydroxyl groups through the quinic acid moiety. Conversely, p-coumaric acid contains only a single phenolic hydroxyl group and therefore exhibits lower radical-scavenging potential. Vanillic acid occupies an intermediate position because the methoxy substituent contributes electron density while reducing hydrogen-bond donor capacity. The expected structure-based antioxidant activity follows the qualitative order: gallic acid > caffeic acid > chlorogenic acid > vanillic acid > p-coumaric acid. This ranking should be interpreted as a structural prediction until supplemented with quantitative antioxidant assay data from the literature or new experiments. A notable inverse relationship was observed between antioxidant potential and predicted drug-likeness (Fig. 1). Increasing hydroxylation generally resulted in higher antioxidant potential, increased HBD and HBA values, larger TPSA values, greater polarity, and reduced predicted membrane permeability. This relationship suggests the existence of an antioxidant activity-drug-likeness trade-off in phenolic acids.

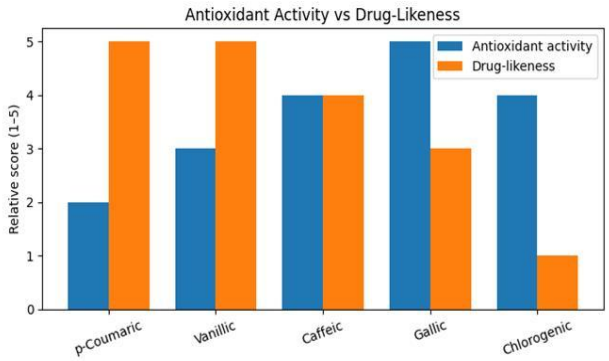


Figure 1. Structure of *p-tert*-butyldihomooxacalix[4]arene tetra(diethyl)amide.

Among the investigated compounds, caffeic acid appears to occupy the most favorable position within the antioxidant activity-drug-likeness landscape. The catechol structure confers strong antioxidant activity, while molecular size, TPSA, and hydrogen-bonding characteristics remain within ranges generally associated with favorable oral absorption. This balance distinguishes caffeic acid from highly permeable but less active compounds and from highly active but more polar compounds.

CONCLUSION

The present study provides a comparative in silico assessment of drug-likeness and antioxidant potential among five representative dietary phenolic acids. The results demonstrate that structural modifications influencing antioxidant activity simultaneously affect physicochemical properties associated with oral absorption. A clear antioxidant activity-drug-likeness trade-off was observed. Increased hydroxylation enhanced predicted antioxidant activity but also increased polarity, hydrogen-bonding capacity, and topological polar surface area. These changes may reduce membrane permeability and pharmacokinetic performance. Among the investigated compounds, caffeic acid exhibited the most favorable balance between antioxidant potential and drug-like properties. This finding suggests that caffeic acid occupies an advantageous position within the structure-property landscape of phenolic acids and may represent a promising scaffold for the development of nutraceutical and pharmaceutical agents.

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