ANTIOXIDANT MECHANISMS OF FLAVONOIDS: STRUCTURE–ACTIVITY RELATIONSHIP (SAR)

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Abstract : *Flavonoids are plant-derived phenolic secondary metabolites synthesized via the phenylpropanoid pathway and characterized by a C6–C3–C6 carbon skeleton. Their antioxidant properties are directly associated with their molecular structure. The present study analyzes the principal structural determinants governing the antioxidant activity of flavonoids and elucidates their radical-scavenging mechanisms. The results indicate that the presence of a 3′,4′-ortho-dihydroxy (catechol) moiety in the B ring, conjugation between the C2–C3 double bond and the 4-oxo functional group, as well as the 3-hydroxyl substituent, enhance electron delocalization and contribute to the stabilization of the corresponding phenoxyl radical. These structural features increase the efficiency of hydrogen atom transfer (HAT) and single electron transfer (SET) mechanisms. The findings support a structure–activity relationship (SAR)-based evaluation of the antioxidant potential of flavonoids and provide a theoretical framework for the rational design of bioactive molecules.*

Keywords: *flavonoids; antioxidant activity; structure–activity relationship (SAR); hydrogen atom transfer (HAT); single electron transfer (SET); radical scavenging.*

INTRODUCTION

In recent years, the role of oxidative stress in various chronic diseases—including cardiovascular pathologies, diabetes mellitus, neurodegenerative disorders, and inflammatory processes—has been extensively investigated [1]. Although reactive oxygen species (ROS) are natural byproducts of cellular metabolism, their excessive generation leads to the oxidative modification of lipids, proteins, and nucleic acids. Therefore, the efficiency of antioxidant defense mechanisms in biological systems is of critical importance [1–3].

Among natural antioxidants, flavonoids occupy a prominent position. Flavonoids are a group of phenolic secondary metabolites synthesized in plants via the phenylpropanoid pathway and characterized by a C6–C3–C6 carbon skeleton. Their biological activity, particularly their antioxidant capacity, is closely associated with the distribution of functional groups within the molecular structure and the electron density pattern [4].

The present study is aimed at elucidating the molecular mechanisms underlying the antioxidant activity of flavonoids and determining the relationship between their structural elements and biological activity.

Research Methodology. The present study was designed to analyze the antioxidant activity of flavonoids based on structure–activity relationship (SAR) principles. The work was grounded in a systematic literature review, examining the correlation between the molecular structure of flavonoids and their radical-scavenging mechanisms. The selected literature encompassed data evaluated by IC_{50} values obtained through DPPH and ABTS assays.

During the analysis, the ortho-dihydroxy moiety in the B ring, the conjugation of the 2,3-double bond with the 4-oxo group, and the presence of a hydroxyl group at the 3-position were assessed as principal structural determinants. The obtained data enabled the interpretation of flavonoids' propensity toward HAT (Hydrogen Atom Transfer) and SET (Single Electron Transfer) mechanisms in relation to their structural features.

Results and Discussion. The manifestation of antioxidant activity depends on the synergistic combination of several structural determinants, which is governed by the degree of electron delocalization within the flavonoid molecule and the reactivity of phenolic hydrogens. In particular, the number and positional distribution of phenolic hydroxyl groups, the presence of a π-conjugated system, and the capacity to form complexes with metal ions exert a significant influence on radical-scavenging efficiency.

In order to systematically elucidate the structure–activity relationship, the principal structural determinants within the flavonoid molecule and their effects on antioxidant mechanisms were summarized in tabular form.

Table 1.

Principal structural determinants governing the antioxidant activity of flavonoids

o.	Structural element	Chemical characteristic	Effect on antioxidant mechanism	General activity trend
	B ring 3′,4′-ortho-dihydroxy (catechol) moiety	Electron-donating, resonance stabilization	Stabilizes the phenoxyl radical (enhanced HAT/SET efficiency)	Associated with high activity

	2,3-double bond + 4-oxo group (C ring)	π-conjugated system	Enhances electron delocalization and increases radical form stability	Increased activity observed
	3-OH group (in flavonols)	Additional hydrogen donor	Enhances radical-scavenging capacity	Moderate–high effect
	5-OH + 4-oxo combination	Metal-chelating capacity	Limits the Fenton reaction via Fe^{2+}/Cu^{2+} chelation	Protective effect present
	Glycosylation (–O-glycoside)	Steric hindrance, reduced –OH reactivity	May decrease HAT/SET mechanism efficiency	Often associated with reduced activity
	Methoxy groups ($–OCH_3$)	Alters electron density	Radical-scavenging capacity may decrease due to reduced number of phenolic –OH groups	Generally decreased activity

The data presented in Table 1 demonstrate that the antioxidant activity of flavonoids is closely associated with specific structural determinants within their molecular architecture. In particular, structures containing a 3′,4′-ortho-dihydroxy (catechol) moiety in the B ring have been reported in the literature to exhibit higher radical-scavenging efficiency. This effect is attributed to enhanced electron delocalization following the formation of the phenoxyl radical.

Moreover, conjugation of the 2,3-double bond with the 4-oxo group in the C ring results in expansion of the π-system and increases the relative stability of the radical form. The hydroxyl group at the 3-position further contributes to antioxidant activity as an additional hydrogen donor.

Overall, it is evident that antioxidant potential is not determined by a single factor but rather depends on the combination of multiple structural elements.

Conclusion. The results of the present study confirm that the antioxidant activity of flavonoids is directly determined by their molecular structure. The most significant structural determinants were identified as the ortho-dihydroxy moiety in the B ring, the conjugation between the 2,3-double bond and the 4-oxo group, and the presence of a 3-hydroxyl group. These elements enhance the efficiency of HAT (Hydrogen Atom Transfer) and SET (Single Electron Transfer) mechanisms.

The elucidation of the structure–activity relationship provides a theoretical framework for the scientifically grounded evaluation of the antioxidant potential of flavonoids, as well as for the rational selection and structural modification of biologically active natural compounds.

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