

## Structure-Radical Scavenging Activity Relationships of Flavonoids

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RECEIVED MARCH 26, 2002; REVISED OCTOBER 4, 2002; ACCEPTED OCTOBER 24, 2002

*Key words*  
flavonoids  
free radical scavenging activity  
structure-activity relationships

The relationship between the structural characteristics of 29 flavonoids and their antiradical activity was studied. The obtained results suggest that the free radical scavenger potential of these polyphenolic compounds closely depends on the particular substitution pattern of free hydroxyl groups on the flavonoid skeleton. The possible mechanism of action of flavonoids lacking B ring OHs as free radical scavengers has been proposed.

### INTRODUCTION

Flavonoids are a group of naturally occurring polyphenolic compounds ubiquitously found in fruits and vegetables.<sup>1</sup> The various classes of flavonoids differ in the level of oxidation of the C ring of the basic benzo- $\gamma$ -pyrone structure. Common family members of flavonoids include flavones, flavanes, flavonols, catechins, and anthocyanidins. For example, anthocyanidins possess the pyrylium structure<sup>2</sup> of the C ring. The structural difference in each flavonoid family results from the variation in the number and substitution pattern of the hydroxyl groups and the extent of glycosylation of these groups.<sup>3</sup>

Flavonoids have shown potential health benefits arising from the antioxidative effects of these phytochemicals, whose properties are attributed to the phenolic hydroxyl groups attached to the flavonoid structure.<sup>4</sup> Scavenging of free radicals seems to play a considerable part in the antioxidant activity of flavonoid compounds. In very recent years, flavonoids as potent free radical scavengers have attracted a tremendous interest as possible therapeutics against free radical mediated diseases.<sup>5</sup> Free rad-

icals are constantly generated *in vivo* both by »accidents of chemistry« and for specific metabolic purposes. When an imbalance between free radical generation and body defense mechanisms occurs, oxidative damage will spread over all the cell targets (DNA, lipids, proteins). It has been reported that a series of human illness such as cancer, atherosclerosis, cardio- and cerebrovascular diseases, diabetes, immune system impairment, neurodegenerative diseases such as Parkinson's and Alzheimer's diseases, and arthritis, as well as premature body aging, can be linked to the damaging action of extremely reactive free radicals.<sup>6</sup> Many phenolics, such as flavonoids, have antioxidant capacities that are much stronger than those of vitamins C and E.<sup>7</sup> Flavonols and flavones are flavonoids of particular importance because they have been found to possess antioxidant and free radical scavenging activity in foods.<sup>8</sup>

Intake of antioxidant compounds present in food is an important health-protecting factor. Flavonoids, which occur both in edible plants and in foodstuffs derived from plants (*e.g.*, fruits and vegetables, red wine, and tea), form substantial constituents of the human diet.

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Therefore, flavonoids given as biological substances in foodstuffs might be applied to the prevention and treatment of human diseases.<sup>9</sup>

### Free Radical Scavenging Activity of Flavonoids

Flavonoid antioxidants function as scavengers of free radicals by rapid donation of a hydrogen atom to radicals. As recently reviewed by Pietta,<sup>10</sup> numerous authors have investigated the antioxidant activity of flavonoids, and many attempts have been made to establish the relationship between flavonoid structure and their radical-scavenging activity.<sup>11–24</sup> In general, the radical-scavenging activity of flavonoids depends on the molecular structure and the substitution pattern of hydroxyl groups, *i.e.*, on the availability of phenolic hydrogens and on the possibility of stabilization of the resulting phenoxyl radicals *via* hydrogen bonding or by expanded electron delocalization.<sup>11,13</sup> Previous structure-activity relationship (SAR) studies of flavonoids have pointed to the importance of the number and location of the phenolic OH groups present for the antiradical efficacy.<sup>13–15,18–21</sup> The structural requirement considered to be essential for effective radical scavenging by flavonoids is the presence of a 3',4'-dihydroxy, *i.e.*, a *o*-dihydroxy group (catechol structure) in the B ring, possessing electron donating properties and being a radical target. Also, the 3-OH moiety of the C ring is also beneficial for the antioxidant activity of flavonoids.<sup>16</sup> The C2-C3 double bond conjugated with a 4-keto group, which is responsible for electron delocalization from the B ring, enhances further the radical-scavenging capacity,<sup>11–18</sup> and saturation of the 2,3-double bond is believed to cause a loss of activity potential.<sup>13</sup> Also, the presence of both 3-OH and 5-OH groups in combination with a 4-carbonyl function and C2-C3 double bond increases the radical scavenging ac-

tivity.<sup>22</sup> In the absence of the *o*-dihydroxy structure in the B ring, hydroxyl substituents in a catechol structure on the A-ring were able to compensate and become a larger determinant of flavonoid antiradical activity.<sup>19</sup> Figure 1 summarizes the structural criteria that modulate the free radical scavenging activity of flavonoids.

In summary, these structural features contribute to the increase of the phenoxyl radical stability, *i.e.*, the radical scavenging activity of the parent flavonoid.

The aim of our study was to elucidate the relationship between the molecular structure of a series of structurally related flavonoids (flavones, flavonols and flavanones) and their ability to scavenge 1,1-diphenyl-2-picrylhydrazyl (DPPH<sup>•</sup>) free radicals. DPPH<sup>•</sup> is a free radical compound and it has been widely used to test the free radical scavenging ability of flavonoids.<sup>25</sup> The scavenging of DPPH<sup>•</sup> by flavonoid (free radical scavenger) can be represented as depicted in Figure 2.

## RESULTS AND DISCUSSION

A series of flavonoids with different substitution patterns was tested to define the molecular features required for a high antiradical activity of these compounds. The set of 29 flavonoid derivatives was taken from a recent paper by Burda and Oleszek.<sup>26</sup> The flavonoids studied exhibit vastly different antiradical activity. Structures of the flavonoids used in the analysis, as well as the experimental values of related free scavenging activities, are shown in Table I.

To ascertain the relationship between chemical structures of the flavonoids and their radical scavenging activities (RSA), various molecular features can be analyzed. Thus far, despite the fact that many studies have been published on the structure-activity relationships of flavonoids as radical scavengers, most of them have only been descriptive.<sup>13</sup> Recently, an attempt was made by Lien *et al.*<sup>21</sup> to develop a quantitative structure-activity relationship (QSAR) model which would correlate the antioxidant capacity of flavonoids with various physicochemical parameters. They used the Trolox equivalent antioxidant capacity (TEAC) as experimental data to determine the hierarchy of radical scavenging abilities of flavonoids. A highly significant correlation was obtained using the number of free phenolic OH groups ( $n_{OH}$ ) and an indicator variable *I*. They defined the indicator variable *I* as the sum of the following molecular features: the pres-

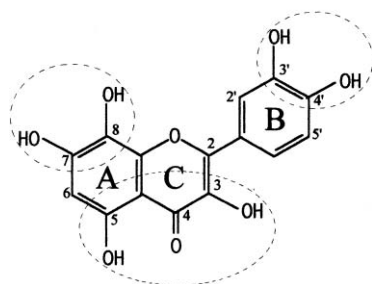


Figure 1. Structural features of flavonoids with a high radical scavenging activity.

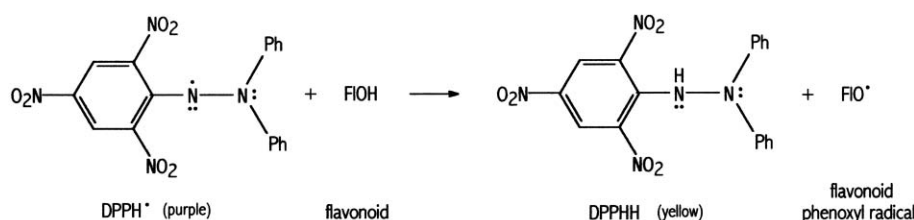
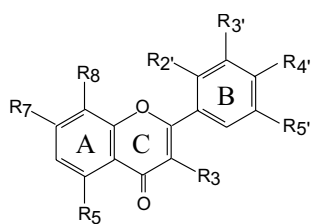


Figure 2. Scavenging of DPPH<sup>•</sup> (free radical) by a flavonoid (free radical scavenger).

TABLE I. Substitution pattern of the series of flavonoids examined for their antiradical activity



No	Compound	RSA <sub>exp.</sub> / % <sup>(a)</sup>	R <sub>3</sub>	R <sub>5</sub>	R <sub>7</sub>	R <sub>8</sub>	R <sub>2'</sub>	R <sub>3'</sub>	R <sub>4'</sub>	R <sub>5'</sub>	C <sub>2</sub> =C <sub>3</sub>
1	morin	96.5	OH	OH	OH	H	OH	H	OH	H	+
2	taxifolin	94.8	OH	OH	OH	H	H	OH	OH	H	–
3	kaempferol	93.5	OH	OH	OH	H	H	H	OH	H	+
4	fustin	91.9	OH	H	OH	H	H	OH	OH	H	–
5	galangin	91.8	OH	OH	OH	H	H	H	H	H	+
6	rutin	90.9	Ogl <sup>(b)</sup>	OH	OH	H	H	OH	OH	H	+
7	quercetin	89.8	OH	OH	OH	H	H	OH	OH	H	+
8	luteolin 7-gl	87.6	H	OH	Ogl	H	H	OH	OH	H	+
9	quercetin 3,7-digl	86.8	Ogl	OH	Ogl	H	H	OH	OH	H	+
10	laricytrin	84.6	OH	OH	OH	H	H	OH	OH	OMe	+
11	laricytrin-3'-gl	83.8	OH	OH	OH	H	H	Ogl	OH	OMe	+
12	robinetin	82.3	OH	H	OH	H	H	OH	OH	OH	+
13	fisetin	79.0	OH	H	OH	H	H	OH	OH	H	+
14	myricetin	72.8	OH	OH	OH	H	H	OH	OH	OH	+
15	kaempferol 3,7-digl	70.6	Ogl	OH	Ogl	H	H	H	OH	H	+
16	3-hydroxyflavone	66.0	OH	H	H	H	H	H	H	H	+
17	apigenin 7-gl	34.8	H	OH	Ogl	H	H	H	OH	H	+
18	hesperetin	30.0	H	OH	OH	H	H	OH	OMe	H	–
19	vitexin	21.0	H	OH	OH	Ogl	H	H	OH	H	+
20	3,5,7,3',4',5'-hexa-methoxyflavone	12.6	OMe	OMe	OMe	H	H	OMe	OMe	OMe	+
21	naringenin	6.3	H	OH	OH	H	H	H	OH	H	–
22	naringin	4.7	H	OH	Ogl	H	H	H	OH	H	–
23	7-hydroxyflavone	2.8	H	H	OH	H	H	H	H	H	+
24	flavanone	2.6	H	H	H	H	H	H	H	H	–
25	flavone	1.5	H	H	H	H	H	H	H	H	+
26	chrysin	1.1	H	OH	OH	H	H	H	H	H	+
27	apigenin	0.7	H	OH	OH	H	H	H	OH	H	+
28	8-methoxyflavone	0.7	H	H	H	OMe	H	H	H	H	+
29	5-hydroxyflavone	0.6	H	OH	H	H	H	H	H	H	+

<sup>(a)</sup>Experimental values as RSA, radical scavenging activity (percents) were taken from ref. 26; <sup>(b)</sup>gl, glycosyl.

ence of the 2,3-double bond ( $I = 1$ ) or two of 3,5,7-OH groups ( $I = 1$ ) or two of 3',4',5'-OH groups ( $I = 1$ ), or the absence of the above situations ( $I = 0$ ). However, application of these molecular descriptors to our flavonoid data set resulted in a poor regression model, Eq. (1):

$$\text{RSA} = -3.045(\pm 11.130) + 13.070(\pm 4.947) n_{\text{OH}} + 9.712(\pm 9.796) I \quad (1)$$

$$n = 29 \quad r = 0.759 \quad s = 26.9 \quad F = 17.6$$

In the above and subsequent equations,  $n$  represents the number of compounds,  $r$  is the multiple correlation coefficient,  $s$  the standard deviation, and  $F$  the ratio of regression and residual variances.

To develop better QSAR models, we initially used a pool of 34 topological and electronic descriptors described in our recent report.<sup>27</sup> However, the obtained RSA models were not particularly good. As a cornerstone for further QSAR modeling, we applied the well known fact that the substitution pattern of phenolic OH

groups on flavonoid core reflects the electron or hydrogen donating ability of flavonoids as radical scavengers.<sup>23</sup> Previous descriptive structure-radical scavenging activity relationships of flavonoids demonstrated that the positions of phenolic OH groups could be more important for the radical scavenging activity than the number of phenolic OH groups.<sup>20,24</sup> In an attempt to improve the RSA model, we employed indicator variables to mark the presence ( $I = 1$ ) or absence ( $I = 0$ ) of phenolic OH groups at any position, *i.e.*, positions 3, 5, 7, 2', 3', 4', or 5', as well as the presence or absence of any particular combination of phenolic OH groups (for example, 3',4'-dihydroxy substitution). Descriptor selections and the corresponding models for structure-activity relationships were performed using the multiple linear regression method. Cross correlation coefficients were used to eliminate colinear descriptors. No colinearity greater than  $\approx 0.40$  was permitted for descriptors in final models.

Multiple regression analysis confirmed that variations in the OH substitution pattern were responsible for variation of the radical scavenging activity of the flavonoids studied. The most predictive model using two independent variables is as follows, Eq. (2):

$$\text{RSA} = 5.936(\pm 5.330) + 71.490(\pm 5.345) I_{3',4'\text{-diOH or }3\text{-OH}} + 11.880(\pm 5.774) I_{5\text{-OH}} \quad (2)$$

$$n = 29 \quad r = 0.938 \quad s = 14.3 \quad F = 95.2$$

where  $I_{3',4'\text{-diOH or }3\text{-OH}}$  and  $I_{5\text{-OH}}$  represent indicator variables. If a particular flavonoid possesses 3',4'-diOH or 3-OH moiety, then value 1 is ascribed to the indicator variable  $I_{3',4'\text{-diOH or }3\text{-OH}}$ , elsewhere 0; similarly, if the flavonoid bears the 5-OH group, value 1 is ascribed to  $I_{5\text{-OH}}$ , elsewhere 0. The improvement over the model given by Eq. (1) is considerable.

Excluding the outlier (compound 15) from the data set, the statistical analysis results in an improved regression equation (3):

$$\text{RSA} = 3.954(\pm 3.556) + 75.950(\pm 3.631) I_{3',4'\text{-diOH or }3\text{-OH}} + 8.499(\pm 3.877) I_{5\text{-OH}} \quad (3)$$

$$n = 28 \quad r = 0.974 \quad s = 9.5 \quad F = 230.7$$

In Figure 3, we give the plot of the predicted radical scavenging activity,  $\text{RSA}_{\text{calcd.}}$  vs. the experimental radical scavenging activity,  $\text{RSA}_{\text{exp.}}$  obtained from Eq. (3). Figure 3 reveals that the 28 flavonoids considered split into two equally populated clusters – 15 highly active flavonoids (with 3-OH and/or 3',4'-diOH) and 13 flavonoids of a rather low activity (without 3-OH and 3',4'-diOH).

On the basis of these results it appears that the most effective radical scavengers are flavonoids with the 3',4'-dihydroxy substitution pattern on the B-ring and/or hydroxyl group at the C-3 position. The presence of a *o*-dihydroxy structure on the B-ring confers a higher degree of stability on the flavonoid phenoxyl radicals by participating in electron delocalization and is an important feature for the antiradical potential.<sup>11</sup> Interestingly, the presence of a double bond between C-2 and C-3 in the C ring seems not to be a prerequisite for antiradical activities. High antiradical activities of the flavanones taxifolin and fustin appeared to be related to the favorable 3',4'-dihydroxy substitution pattern on the B-ring. The lowest antiradical scavenging flavonoids lack both the C-3 hydroxyl group and the 3',4'-dihydroxy occupied B ring.

Van Acker *et al.*<sup>16</sup> report that the catechol moiety in combination with a C2-C3 double bond and a 4-keto function are the essential structural elements for a potent

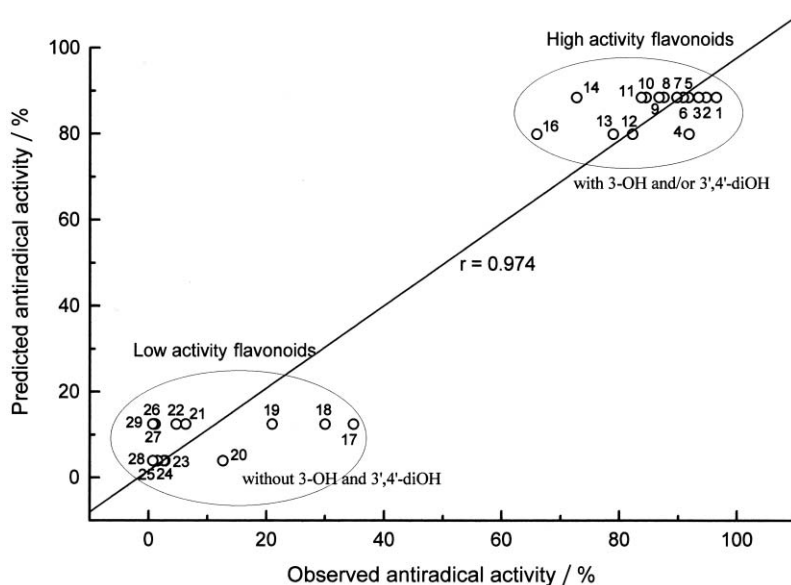


Figure 3. Plot of the predicted radical scavenging activity,  $\text{RSA}_{\text{calcd.}}$  vs. experimental radical scavenging activity,  $\text{RSA}_{\text{exp.}}$ .

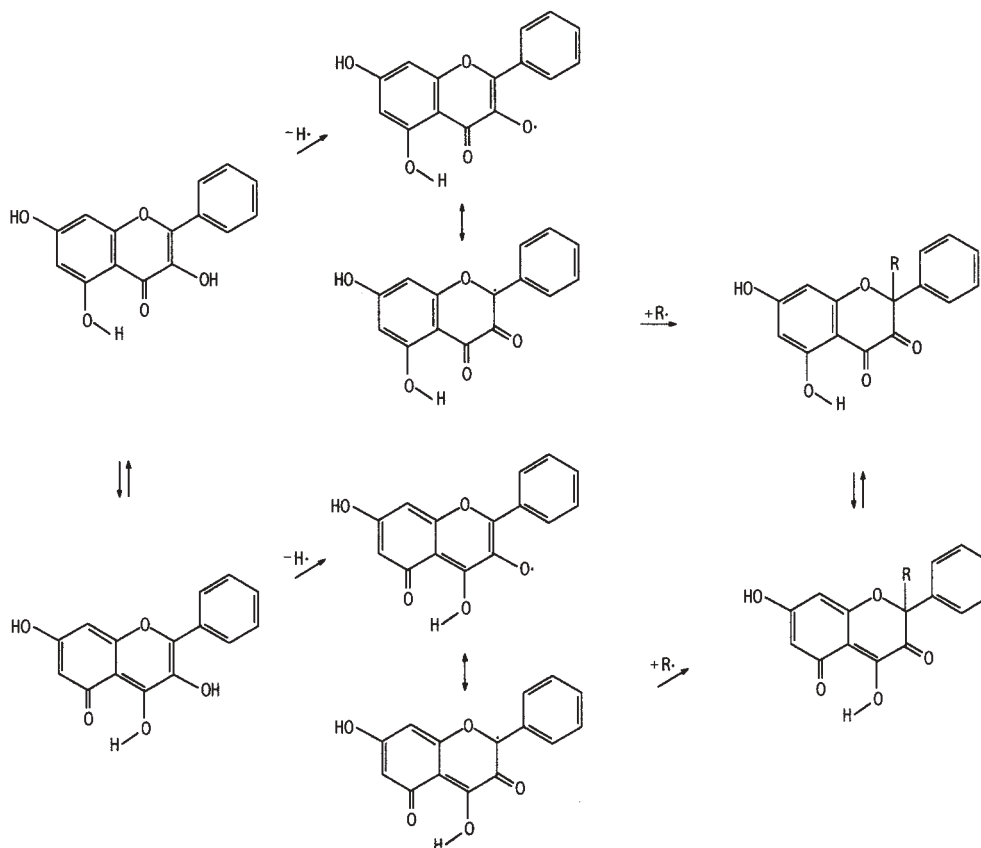
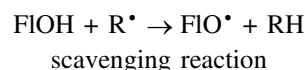


Figure 4. Mechanism of the radical scavenging activity of galangin.

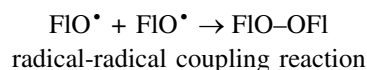
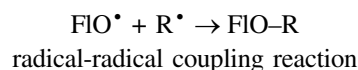
antioxidant activity. We have shown with the studied series of compounds that this is not necessarily true, as flavanols – without the C2-C3 double bond, are among the most potent compounds. The C2-C3 double bond is not necessary for a high activity, but the presence of a 3-OH group significantly enhances the antioxidant activity.

In flavonoids that have only one OH in ring B or none at all, the rest of the flavonoid appears to become more important for the scavenging activity than in the case of catechol flavonoids. The flavonol galangin, which lacks hydroxyl substitution at the B-ring, demonstrated high activity. This is probably caused by the combination of the C2-C3 double bond with the 3-OH. Flavonoids which lack catechol OHs on ring B, but possess a 3-OH next to the 4-keto group, show a high scavenging activity.

There is much discussion in the literature about the mechanisms of the antioxidative action of flavonoids.<sup>28</sup> Until now, these mechanisms and structural requirements have not been fully understood. As polyphenolic compounds, flavonoids have the ability to act as antioxidants by a free radical scavenging mechanism with the formation of less reactive flavonoid phenoxyl radicals.<sup>19</sup> The high potential of flavonoid compounds (FIOH) to scavenge free radicals ( $R^\bullet$ ) may be explained by their ability to donate a hydrogen atom from their hydroxyl group and thereby scavenge the free radicals:



This reaction gives the flavonoid phenoxyl radicals ( $\text{FIO}^\bullet$ ) and a stable molecule (RH).  $\text{FIO}^\bullet$  subsequently undergoes a change to a resonance structure by redistributing the unpaired electron on the aromatic core. Thus, flavonoid phenoxyl radicals exhibit a much lower reactivity compared to  $R^\bullet$ .  $\text{FIO}^\bullet$  would react further to form unreactive compounds, probably by radical-radical termination:



Combining the above with the obtained results from the modeling procedure, one could suggest the possible mechanism of free radical scavenging of flavonoids lacking OHs on ring B. For example, it seems that galangin (3,5,7-trihydroxyflavone) could easily donate a 3-hydroxyl hydrogen and form the 3-flavonoid phenoxyl radical. This is in agreement with the literature data: for example, in the case of quercetin abstraction of 3-OH

hydrogen leads to a more stable radical tautomer.<sup>29</sup> Consequently, the formed phenoxyl radical undergoes resonance stabilization. Moreover, as very recently reported by Heijnen *et al.*,<sup>22</sup> intramolecular rearrangement may take place when the 5-OH group is present, giving a catechol-like structure in ring C. According to the published results,<sup>30,31</sup> and our calculations using the standard form of the HMO method (superdelocalizability indices for radical attack), position 2 of flavonoid phenoxyl radicals is one of the most suitable centres for the unpaired electron, *i.e.*, more susceptible to radical attack. In this case, the radical-radical termination reaction may be probable in position 2. A hypothetical reaction mechanism for the radical scavenging activity of galangin is represented in Figure 4.

This mechanism illustrates a possible mode of action for flavonoids lacking 3',4'-diOH substitution. Thus, it seems that the famous *o*-dihydroxy (catechol) structure in the B ring is not always a *conditio sine qua non* in achieving high free radical scavenging activity of flavonoids. The presented consideration is in agreement with other studies that suggested that the 3-OH group is a significant contributor to high antiradical activity.<sup>16,19,23,29</sup> Our study may provide some additional insight into the free radical scavenging actions of flavonoids.

## CONCLUSION

We have shown in this work that the use of simple indicator variables embracing OH groups of flavonoid core makes it possible to build reliable QSARs.<sup>32</sup> The developed structure-antiradical activity relationship (given by Eq. 3) indicates that highly active flavonoids possess a 3',4'-dihydroxy occupied B ring and/or 3-OH group. Analysis of flavonoid QSARs has offered an insight into their possible mechanisms of action, and we have proposed a mode of action for flavonoids lacking 3',4'-diOH groups. We hope that the presented QSARs will be instrumental in the design of new flavonoid based drugs for the treatment of free radical mediated disease conditions.

*Acknowledgement.* – This work was supported in part by Grants 0079025 (D.A., D.D.A., D.B.) and 0098034 (N.T.) awarded by the Ministry of Science and Technology of the Republic of Croatia. We thank the reviewers for their constructive comments.

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32. In our forthcoming reports we will discuss the predictive ability of CODESSA and DRAGON programs in the modeling of flavonoid QSARs.

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## SAŽETAK

### Odnos između strukture flavonoida i njihova hvatanja slobodnih radikala

Dragan Amić, Dušanka Davidović-Amić, Drago Bešlo i Nenad Trinajstić

Proučavan je odnos između strukturnih svojstava 29 flavonoida i njihove antiradikalne aktivnosti. Dobiveni rezultati pokazuju da je djelotvornost tih polifenolnih spojeva kao hvatača slobodnih radikala u biti uvjetovana rasporedom slobodnih hidroksilnih skupina na flavonoidnoj jezgri. Za flavonoide koji nemaju OH-skupine na prstenu B predložen je mogući mehanizam hvatanja slobodnih radikala.