Med Chem Res
DOI 10.1007/s00044-008-9151-y

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

QSAR modeling of anthocyanins, anthocyanidins and catechins as inhibitors of lipid peroxidation using three-dimensional descriptors

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Received: 26 June 2008 / Accepted: 25 November 2008

Abstract This work describes the quantiative structure–activity relationship (QSAR) study of lipid peroxidation inhibitory effect of catechins, anthocyanidins and anthocyanins using molecular descriptors and physicochemical parameters derived from optimised three-dimensional (3D) structure, since this set of studied compounds contains stereoisomers with different activities. Six groups of 3D descriptors have been used to generate QSAR models: geometrical, 3D molecule representation of structures based on electron diffraction (3D-MoRSE); Randic molecular profiles; geometry, topology and atom weights assembly (GETAWAY); radial distribution function (RDF); and weigthed covariance matrices (WHIM) descriptors. The 3D molecular descriptors and physicochemical parameters have been calculated applying the online software Parameter Client and HyperChem 8.0. The primary selection of 3D molecular descriptors and physicochemical parameters was based on their ability to discriminate stereoisomers. Further selection of predictor variables for multiple regression was performed by the best-subset and forward stepwise method. The best-developed QSAR models consisted of geometrical, RDF and Randic molecular profiles descriptors. Those descriptors could be used for the prediction of the biological activity of catechin stereoisomers and their derivates. The obtained models suggest that the inhibitory effect of studied compounds is related to the shape of the molecule and the three-dimensional distribution of atomic mass in the molecule.

Keywords QSAR · 3D descriptors · Flavonoids · Lipid peroxidation

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Published online: 23 December 2008

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Introduction

Catechins, anthocyanidins and their glycosides—anthocyanins, compounds that belong to the natural antioxidants the flavonoids, present in foods of plant origin, are potentially beneficial to human health. Antioxidative effects of those phytochemicals are based on free-radical scavenging or the protection of biological molecules against oxidation (Rice-Evans *et al*., 1996). Many studies have shown that increased dietary intake of flavonoids, especially moderate, prolonged red wine consumption, is correlated with reduced incidence of coronary heart disease. Some studies have related this protective effect of flavonoids to their ability to inhibit the oxidation of human low-density lipoproteins (LDL) (Frankel *et al*., 1995; Hertog *et al*., 1993).

Flavonoids are benzo-γ-pirone derivates with a basic stucture that consists of 15 carbon atoms arranged in three rings. The structural differences in each flavonoid family result from variation in the number/substitution pattern of the hydroxyl and methoxy groups, as well as different glycosylation patterns. These structural variations are responsible for differences in antioxidant activities of flavonoid compounds (Amić *et al*., 2007).

Relatively few quantitative structure–activity relationship (QSAR) studies involving the flavonoids as inhibitors of lipid peroxidation (LPO) have been reported. Different descriptors were used to develop a QSAR models and they usually include parameters accounting for electronic properties, hydrophobicity, topology and steric effects. Thereby, Rackova *et al*. (2005) obtained the best model for the antioxidant activity with hydration energy (E_{HYDR}) ($r = 0.747$, $n = 12$). In the study of Rasulev *et al*. (2005), various two-dimensional (2D) and three-dimensional (3D) descriptors calculated by DRAGON program, quantum-chemical descriptors and several indicator variables were used to generate QSAR models for LPO of 27 flavonoids. One of the best developed QSAR models ($r = 0.935$, $n = 27$) consists of four descriptors: geometrical descriptor *PJI3* (Petitjean shape index), an electronic descriptors μ (dipole moment) and two indicator descriptors: the presence or absence of the OH group at the C-3 position (I_{OH}) and presence or absence of OCH_3 group at the C-3′ position in the B ring (I_{Glc}). In the recent study of Ray *et al.* (2008), QSAR modeling for LPO inhibition potential of flavonoids has been carried out using topological, structural and electrotopological-state atom (E-state) indices.

Generally, there is a lack of published, well-defined QSAR studies for the data set of flavonoids that includes stereoisomers, such as (+)- and (−)-catechin, or (+)- and (−)-epicatechin. The study of Yang *et al*. (2001) showed that LPO inhibiting effect of flavonoids strongly depends on the stereochemistry. The obtained two-descriptor QSAR model for the antioxidant activities of studied compounds includes half-wave potential of the first oxidation wave measured by flow-through column electrolysis ($E_{1/2}$) and octanol/partition coefficients (log P) calculated by software ($r = 0.852$, $n = 23$). Since both variables are not derived from three-dimensional structure and do not distinguish stereoisomers, these facts considerably lower the correlation factor and make both parameters worthless for QSAR study of the mentioned data set.

A recent study has evaluated inhibition of LPO of series catechins, anthocyanins and anthocyanidins (Seeram and Nair, 2002). Structure–activity relationship (SAR) studies have shown that the number of hydroxyl substituents present on the B-ring,

the presence of methoxyl groups and the number of sugar residues are important criteria for antioxidant activity of anthocyanidins. For catechins, critical determinant of antioxidant activity is a 3′,4′-dihydroxy moiety in the B ring. However, the effects of *cis–trans* isomerization, epimerization and racemization on small, but significant, differences between antioxidant activities of catechins could not be elucidated by SAR study. The purpose of the present paper was to find more representative 3D descriptors able to discriminate stereoisomers of catechins. The intention was also to develop QSAR models for LPO inhibitory effect of the aforementioned set of compounds using selected molecular descriptors and physicochemical parameters. The obtained results should give a contribution for better understanding of the free-radical-scavenging ability of flavonoids.

Materials and methods

Biological activity

In the present study we used the data set of 21 flavonoids with antioxidant activities reported in work of Seeram and Nair (2002). The antioxidant activities of 5 anthocyanidins, 5 anthocyanins and 11 catechins were evaluated in terms of their abilities to inhibit lipid peroxidation induced by Fe(II) ions in liposomal model. The rate of peroxidation was monitored by decrease in fluorescence intensity as a function of time. Inhibition of LPO is given as relative fluorescence (F_t/F_0) calculated by dividing the fluorescence value at the given point (F_t) at $t = 0$ min (F_0), expressed as a logarithm of the percentage of LPO inhibition (log I_{LPO}). Structural details and biological activities of anthocyanidins and anthocyanins used in this study are given in Table 1, and those of catechins in Table 2.

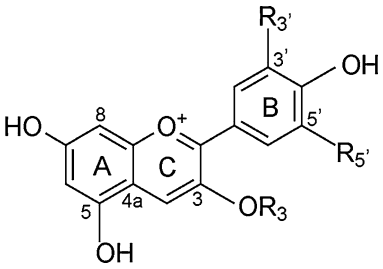
Generation of physicochemical properties and molecular descriptors

ISIS/Draw 2.3 software (MDL Information System, Inc.) was used to draw 2D structures of molecules. The 3D structures were optimised using the molecular mechanics force fields (MM+) applying the HyperChem 8.0 Evaluation software package (Hypercube Inc.). Subsequently, all structures were submitted to the geometry reoptimization using semiempirical AM1 method, applying the Polak–Ribiere conjugate gradient with unrestricted Hartree-Fock (UHF) method spin pairing, 0.1 convergence limit in vacuo and root-mean-square (RMS) gradient of 0.001 kcal/Å mol.

After geometry optimization, several physicochemical parameters were calculated with HyperChem: the energy of the highest occupied molecular orbital (E_{HOMO}), the energy of the lowest unoccupied molecular orbital (E_{LUMO}), the difference between E_{HOMO} and E_{LUMO} (GAP), the heat of formation (H_f), hydration energy (E_{HYDR}), volume (V) and surface (S) of the molecule.

Simplified molecular input line entry system (SMILES) notations, created online by Demo-CONVERT Interactively (Molecular Networks GmbH, http://www.molecular-networks.com/online_demos/convert_demo.html), were used as a chemical

Table 1 Structural details of anthocyanidins and anthocyanins with their effects on the rate of the lipid peroxidation (I_{LPO})



No.	Compound	$R_{3'}$	$R_{5'}$	R_3	log I_{LPO}
1	Delphinidin	OH	OH	H	1.847
2	Cyanidin	OH	H	H	1.779
3	Malvidin	OMe	OMe	H	1.636
4	Peonidin	OMe	OH	H	1.654
5	Pelargonidin	H	H	H	1.606
6	Delphinidin-3-galactoside	OH	OH	Galactose	1.639
7	Cyanidin-3-galactoside	OH	H	Galactose	1.545
8	Cyanidin-3-rutinoside	OH	H	Rutinose	1.467
9	Cyanidin-3-glucosylrutinoside	OH	H	Glucose-rutinose	1.398
10	Pelargonidin-3-galactoside	H	H	Galactose	1.436

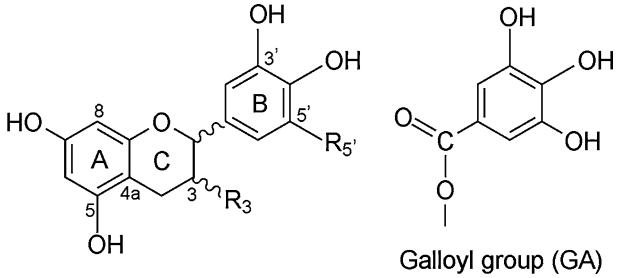
structure input for calculation of 3D molecular descriptors. The 3D molecular descriptors used in this study have been calculated applying the online software Parameter Client (PCLIENT) (http://146.107.217.178/lab/pclient/). PCLIENT is an extension of E-Dragon, an electronic remote version of Dragon program (Tetko *et al*., 2005). Six groups of 3D descriptors were used to generate QSAR models: geometrical, 3D-MoRSE, Randic molecular profiles, GETAWAY, RDF and WHIM descriptors (Todeschini and Consonni, 2000).

Selection of descriptors and statistical analysis

The statistical analysis was performed using STATISTICA 6.0 (StatSoft, Inc.). Relationship between 3D descriptors, physicochemical properties and antioxidant activities of flavonoids was investigated by simple linear and multiple regression analysis. To test quality and accuracy of derived models, the following statistical parameters were used: squared correlation coefficient (r^2), standard deviation of regression (s) and ratio of regression and residual variances (F).

The best possible QSAR models, which are presented in this paper, were selected on the basis of the highest correlation coefficients and F-ratio, as well as the lowest standard deviations. The selected models were additionally validated by the calculation of quality factor (Q). The quality factor Q is defined as a ratio of

Table 2 Structural details of catechins with their effects on the rate of the lipid peroxidation (I_{LPO})



No.	Compound	Symbol	Configuration	R_3	$R_{5'}$	log I_{LPO}
11	(+)-Catechin	(+)-C	2R, 3S	OH	H	1.787
12	(−)-Catechin	(−)-C	2S, 3R	OH	H	1.816
13	(±)-Catechin	(±)-C	2R, 3S; 2S, 3R	OH	H	1.778
14	(+)-Epicatechin	(+)-EC	2S, 3R	OH	H	1.772
15	(−)-Epicatechin	(−)-EC	2R, 3R	OH	H	1.796
16	(−)-Catechin gallate	(−)-CG	2S, 3R	GA	H	1.013
17	(−)-Epicatechin gallate	(−)-ECG	2R, 3R	GA	H	1.114
18	(−)-Gallocatechin	(−)-GC	2S, 3R	OH	OH	1.528
19	(−)-Epigallocatechin	(−)-EGC	2R, 3R	OH	OH	1.534
20	(−)-Gallocatechin gallate	(−)-GCG	2S, 3R	GA	OH	1.464
21	(−)-Epigallocatechin gallate	(−)-EGCG	2R, 3R	GA	OH	1.064

correlation coefficient to the stadard deviation: $Q = r/s$, and is used for accounting predictive power of the model (Pogliani, 1996).

The initial number of 729 calculated molecular indices and physicochemical properties was reduced to 467 descriptors using the following criteria: only those 3D molecular descriptors and physicochemical parameters with ability to discriminate stereoisomers were chosen for regression analysis. Further selection of predictor variables was performed by the best-subset method. The criterion used to determine "best" was based on the values of the squared correlation coefficient (r^2) of analyzed models. Therefore, all-possible-subset regression was carried out on each of the six groups of 3D descriptors and the group of physicochemical properties. Descriptors involved in the 30 best triparametric, diparametric and monoparametric models were used as the new set of 48 independent variables for the final estimation of log I_{LPO}. Further finding of the best models was performed on the remaining set of descriptors by the combination of the forward stepwise method and best-subset method. The number of descriptors in the multiple regression equations was limited to three, considering that the number of compounds in the data set is 21. The terminal selection of the models was based on the intercorrelation study between variables included in the equation. Models with highly collinear descriptors ($|r| \geq 0.7$) were not considered.

Results and discussion

As mentioned above, the numbers of 3D descriptors and properties were calculated for the QSAR study of 21 flavonoids with lipid peroxidation inhibitory activities. The large set of 3D descriptors has been obtained by Parameter Client program after geometry optimization. However, large numbers of those descriptors were not capable of correct prediction of stereoisomer activity because they have equal values for different stereoisomers. Although degeneracy among 3D descriptors may be common for compounds with very similar activities, in this study those descriptors were not used for model development, in spite of the slight, but significant, difference between antioxidant activities of stereoisomers. For the same reason, partial charges, lipophilicity, refractivity and polarizability were excluded from the set of calculated physicochemical descriptors.

After selection of descriptors based on ability to discriminate stereoisomers and applying the best-subset method as the model building technique, the initial number of descriptors was reduced to 48. Selected descriptors for model generation are summarised in the Table 3.

Stepwise regression resulted in the following monoparametric, statistically significant model using the *QXXm* descriptor:

$$\begin{aligned} \log I_{\mathrm{LPO}} &= 1.9695(\pm 0.07) - 0.0043(\pm 0.0006)QXXm \\ n &= 21, r^2 = 0.695, s = 0.133, F = 43.24, Q = 6.26 \end{aligned} \quad (1)$$

QXXm (*QXX* COMMA2 value) is geometrical descriptor that represents the shape of a molecule including the second-order-based geometric moments of the

Table 3 Brief description of selected 3D descriptors and physicochemical properties

Groups of descriptors	Description of molecular descriptors	Number of descriptors
Geometrical	Sum of geometrical distances between oxygen atoms; Qxx COMMA2 value; absolute eigenvalue sum on geometry matrix; 3D Petitjean shape index; average distance/ distance degree	8
3D-MoRSE	3D-MoRSE/unweighted and weighted by: atomic polarizabilities and atomic Sanderson electronegativities	10
Randic molecular profiles	Molecular profile, shape profile	4
GETAWAY	H autocorrelation; R autocorrelation; leverage-weighted autocorrelation; Randic-type R matrix connectivity	4
RDF	Radial distribution function/unweighted, weighted by: atomic masses and atomic Sanderson electronegativities	11
WHIM	Component symmetry directional WHIM index; *V* total size index	7
Physicochemical properties	Surface area/grid and approximate; volume of the molecule; heat of formation	4

3D-MoRSE molecule representation of structures based on electron diffraction, *GETAWAY* geometry, topology, and atom weights assembly, *RDF* radial distribution function, *WHIM* weighted covariance matrices descriptors

property field density, which is obtained by mapping the atomic masses at the atomic position (Silverman, 2000). The principal component *QXXm* is defined to be invariant with reference to the principal geometric *X*-axis located at the molecular centroid, therefore allowing proper characterization the shape of each structure along this orientation. Consequently, this descriptor is extremely sensitive to conformational changes and possess the ability for the discrimination of stereoisomers. Due to the negative value of *QXXm* descriptor in Eq. 1 it is expected that stereoisomers with higher value of *QXXm* will have lower activity.

Selecting the independent variables using the best-subset method, the best diparametric model was obtained with geometrical descriptor, *SEig* and radial distribution function (RDF) descriptor, *RDF040m*:

$$\begin{aligned} \log I_{\mathrm{LPO}} &= 2.8656(\pm 0.1438) - 0.0134(\pm 0.0015)SEig \\ &\quad + 0.0024(\pm 0.0006)RDF040m \\ n = 21, r^2 &= 0.827, s = 0.100, F = 43.103, Q = 9.1 \end{aligned} \tag{2}$$

SEig is an absolute eigenvalue sum on geometry matrix. This index, derived from geometry-sensitive matrices, is the measure of molecular folding, namely, the departure of the molecular structure from a strictly linear chain, so it is appropriate for discrimination of stereoisomers (Randić *et al*., 1994). The value of this index decreases with the degree of departure from linearity. Hence, more "linear" molecules (or stereoisomers), even if of larger size, have larger values of *SEig*, and according to Eq. 2, they are more inactive than the folded molecules (or stereoisomers).

Radial distribution functions are molecular descriptors obtained by the transformation of 3D coordinates of atoms into the structure code that has a fixed number of descriptors, irrespective of the size of a molecule. The RDF of an ensemble of *N* atoms can be interpreted as the probability distribution to find an atom in a spherical volume of radius *r* (Hemmer *et al*., 1999). The presence of the *RDF040m* descriptor in Eq. 2 suggests the occurrence of some linear dependence between the LPO inhibitory activity and the 3D molecular distribution of mass, calculated at radius of 4.0 Å from the geometrical centers of each molecule.

Best-subset regression indicated that an additional descriptor, *DPO9*, can be added to Eq. 2 to further improve the statistics:

$$\begin{aligned} \log I_{\mathrm{LPO}} &= 2.8049(\pm 0.1399) - 0.0126(\pm 0.0015)SEig \\ &\quad + 0.0028(\pm 0.006)RDF040m - 0.0010(\pm 0.0006)DP09 \\ n = 21, r^2 &= 0.855, s = 0.092, F = 33.32, Q = 10.043 \end{aligned} \tag{3}$$

The plot of the observed versus calculated I_{LPO} values generated from Eq. 3 is shown in Fig. 1. Observed and calculated log I_{LPO} values using Eq. 3, with associated residuals, are given in Table 4. As can be seen, calculated values are very close to the observed values.

Involving the Randić molecular profile descriptor no. 09 (*DPO9*) as a third variable in Eq. 3 resulted in the slight increase of r^2 from 0.827 to 0.855. Randić molecular profile descriptors were calculated from the geometric interatomic

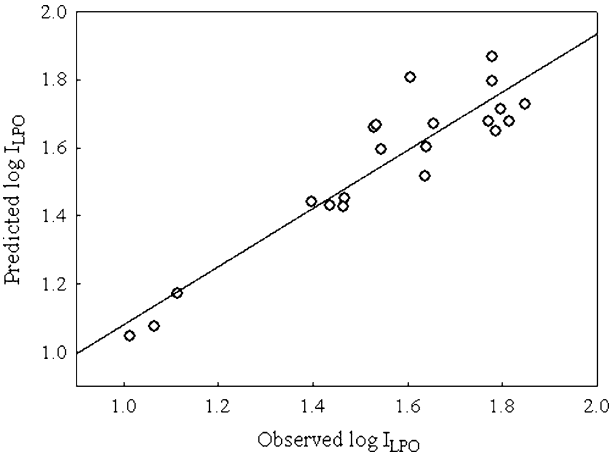


Fig. 1 Observed versus and calculated log I_{LPO} values from Eq. 3. log I_{LPO} is the logarithm of the percentage inhibition of lipid peroxidation

Table 4 Observed and calculated log I_{LPO} values using Eq. 3 with associated residuals

Compound no.	Observed log I_{LPO}	Calculated log I_{LPO}	Residual
1	1.847	1.727	0.120
2	1.779	1.795	−0.016
3	1.636	1.515	0.121
4	1.654	1.671	−0.017
5	1.606	1.807	−0.201
6	1.639	1.601	0.038
7	1.545	1.594	−0.049
8	1.467	1.453	0.014
9	1.398	1.442	−0.044
10	1.436	1.432	0.004
11	1.787	1.649	0.138
12	1.816	1.679	0.137
13	1.778	1.869	−0.091
14	1.772	1.678	0.094
15	1.796	1.714	0.082
16	1.013	1.046	−0.033
17	1.114	1.173	−0.059
18	1.528	1.658	−0.130
19	1.534	1.665	−0.131
20	1.464	1.426	0.038
21	1.064	1.076	−0.012

distance for all atoms at the atomic periphery. They characterise molecular shape in the form of a shape profile. Mentioned descriptors fully reflect the symmetry of shapes, and are extremely sensitive to stereoisomerism (Randić and Razinger,

Table 5 Correlation matrix for the descriptors included in the Eqs. 2 and 3

	SEig	*RDF040m*	*DP09*
SEig	1.00		
RDF040m	0.64	1.00	
DP09	0.60	0.66	1.00

1995). Consequently, these descriptors can be used to generate the QSAR models for data sets containing the steroisomers, such as the set of flavonoid compounds in the present study.

We obtained a correlation matrix between all descriptors concerned in final selection of models, because the regression equation is useless and difficult to interpretat when the predictor variables are highly mutually correlated. The correlation matrix (Table 5) shows that the descriptors included in Eqs. 2 and 3 are independent.

The derived QSAR models indicate the relevance of shape of molecules and three-dimensional distribution of mass on LPO inhibitory activity of flavonoids. In the study of Rasulev *et al.* (2005), QSAR models developed using Petitjean shape index have evidenced that the shape of flavonoid molecules plays an important role on their inhibition of lipid peroxidation potential. Our recent QSAR study of inhibitory effect of wine polyphenols on lipid peroxidation has also confirmed the considerable influence of size, mass and shape of molecules on that kind of activity (Rastija and Medić-Šarić, 2008).

It is well known that many physical, chemical, or biological properties of compounds are dependent on the three-dimensional arrangement of atoms in a molecule, and that many biochemical processes are stereospecific. So, the analysis of such structure–property relationship should take into account the 3D structure of studied molecules (Schuur *et al.*, 1996; Golbraikh and Tropsha, 2003; Vračko and Gasteiger, 2002). Application of descriptors derived from 3D representation of molecules in this study has been necessary since the set of studied compounds containes a few stereoisomers with different activities. Some of the involved descriptors were proved to be extremely sensitive to stereoisomerism. Their discrimination of stereoisomers is based on: difference in the three-dimensional distribution of atomic mass (described by *QXXm* and *RDF040m*), or difference in the shape of molecules (described by *SEig* and *DPO9*).

Conclusion

The QSAR models for the lipid peroxidation inhibitory effect of 21 flavonoids have been obtained by the application of three-dimensional descriptors. The best simple linear model was obtained with a geometrical descriptor, and the best multiple linear models, with geometrical, RDF and Randić molecular profile descriptors. The selected descriptors effectively discriminate stereoisomers which were included in the studied data set. The resulting models showed that the shape of the molecule and

the three-dimensional distribution of atomic mass in the molecule have considerably effect on lipid peroxidation inhibition potentital of flavonoid compounds.

Acknowledgements This work was supported by Grants No. 0061117-1237 (M. M.-Š.) and 079-0000000-3211 (V. R.) awarded by the Ministry of Science, Education and Sport of the Republic of Croatia.

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