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Quantitative Modeling of Flavonoid Glycosides Isolated from *Paliurus spina-christi* Mill.

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Several QSPR models for predicting the properties of flavonoid glycosides isolated from *Paliurus spina-christi* Mill. and of some related flavonoids were described and evaluated. Log *P* values for all of them were calculated according to the method of Rekker. All investigated flavonoids showed expressive hydrophobicity. Significant correlation between the partition coefficient, log *P*, and van der Waals volume, V_w (calculated according to the method described by Moriguchi[34] *et al.*) was obtained. Topological indices used for correlation analysis include the Wiener index, *W*(G), valence connectivity index, χ^v(G), Balaban index, *J*(G), and information-theoretic index, *I*(G). The best models were obtained with the valence connectivity index for all the flavonoids studied.

INTRODUCTION

Paliurus spina-christi Mill. /Rhamnaceae/ is a perennial thorny shrub widely spread over dry and rocky parts of the Mediterranean region and Asia. In Croatia, this plant grows along the Adriatic coast and on the islands.[1,2]

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Paliurus spina-christi Mill. grows up to a height of 3 m with greyish-brown to dark brown bark. On the branches small spines are arranged in opposite positions: one spine is long and flat and the other is short and bent. The oval, smooth and asymetric leaves with three costae are alternately arranged. Leaves are 2.0–4.0 cm long and 1.5–3.0 cm wide. Numerous small, yellowish flowers bloom in clusters on the axils in June. Fruits are wooden and discus, 1.5–3.0 cm wide; they are yellow-green in summer and turn brown in autumn.[2]

In our traditional herbal medicine this plant is called »drača« and is used as a diuretic, against diarrhoea and rheumatism.[3,4] Six flavonoid glycosides were isolated from the leaves of *Paliurus spina-christi* Mill.

The isolated flavonoids were characterized as quercetin 3-*O*-glucoside (isoquercitrin), quercetin 3-*O*-rhamnoglucoside (rutin), quercetin 3-*O*-rhamnoglucoside 7-*O*-rhamnoside, scoparin 7-*O*-rhamnoglucoside, kaempferol 3-*O*-rhamnoglucoside 7-*O*-rhamnoside and quercetin 3-*O*-rhamnoglucoside 4'-*O*-glucoside.[5–7]

In this work, several quantitative QSPR models for predicting the properties (especially n-octanol/water partition coefficients and van der Waals volumes) of flavonoids isolated from the above-mentioned plant will be described and evaluated. The models are used in scientific work to represent, predict or estimate phenomena of interest. They are simply approximations of real systems primarily developed for the purpose of prediction. Mathematical models that relate some chemical, biological, or environmental activity of interest to some quantitative structural descriptor or physicochemical property are collectively known as quantitative structure-activity relationships (QSAR) models.[8,9] QSAR models are usually developed for a group of structural congeners. In QSAR approach, molecular structure is described by a number of parameters which can be calculated from molecular topology, *e. g.* topological indices.[9,10] Topological indices like nonempirical structural parameters are convenient tools for formulating direct relationships between the chemical structure and physical, chemical, biological and environmental properties of molecules.[9,11]

METHODS

Calculation of Partition Coefficient (log P)

The n-octanol/water partition coefficient is an empirical parameter and can be calculated by the Hansch[12] or Rekker[13] methods. Log *P* values for all flavonoids were calculated according to the method of Rekker[13] using the equation:

$$\log P = \sum_{i=1}^{n} a_n f_n \quad (1)$$

where a is a numerical factor indicating the incidence of a given fragment f in the structure.

Calculation of Topological Indices

In this work, we have investigated whether four topological indices (the Wiener index, the valence connectivity index, the Balaban index and the information-theoretic index) are applicable to QSAR studies of flavonoids. The majority of topological indices are related either to the adjacency relationship (atom-to-atom connectivity) or to the topological distance (the number of bonds between a pair of atoms) in molecular structure.

Thus, they can be calculated either from the adjacency or from the distance matrix of a chemical graph.

Routinely, they are computed using the graph-theoretical methodology by treating the hydrogen supressed molecular structures in the prescribed way.[9] All indices used in the modeling procedure described in the following section were calculated by the MOLSTRU program for PC computers.[14] Minimum hardware and software requirements for the PC version of MOLSTRU are 2 MB of RAM memory and one double sided/double density disk drive, plus a PC-DOS or MS-DOS operating system version 5.0 or higher.

The Wiener Index, W(G)

The Wiener index $W(G)$[15] of a structure G can be simply obtained from the distance matrix $\boldsymbol{D}$ of the corresponding hydrogen-depleted chemical graph G as half-summation of the elements of $\boldsymbol{D}$:[16]

$$W(G) = \frac{1}{2} \sum_{i,j} (D)_{ij} \quad (2)$$

where $(D)_{ij}$ represent off-elements of $\boldsymbol{D}(G)$ which stand for the shortest distance in terms of the number of bonds between atoms i and j in G. The distance i–j can also be weighted in the case of heteroatomic systems.[17] In the cases studied, all the structures considered are depicted by weighted graphs.

The Valence Connectivity Index, $\chi^v(G)$

The molecular connectivity index, $\chi(G)$ of molecular graph G, was defined by Randić:[18]

$$\chi(\mathrm{G}) = \sum_{\text{edges}} [d(i)\, d(j)]^{-0.5} \tag{3}$$

where the sum is taken over all edges of G, while $d(i)$ and $d(j)$ are valencies of vertices i and j, making up the i–j.

In the case of heterosystems, the connectivity index is given in terms of valence delta values $\delta(i)$ and $\delta(j)$ of atoms i and j, and it is denoted by χ^{v}. This version of connectivity index is called the valence connectivity index and is defined as:[9,14,18–22]

$$\chi^{\mathrm{v}}(\mathrm{G}) = \sum_{i,j} [\delta(i)\, \delta(j)]^{-0.5} \tag{4}$$

where the sum is taken over all bonds i–j of the molecule. In this case each edge of G has a weight of $\delta(i)\ \delta(j)$. The edge weights were taken from the references.[9,22]

The Balaban Index, J(G)

Balaban[23] proposed a topological index, *i. e.* the Balaban index,[17] which represents extended connectivity. This index, denoted by $J(\mathrm{G})$, is defined as:[24]

$$J(\mathrm{G}) = \frac{M}{\mu + 1} \sum_{\text{edges}} (\mathrm{ds_i}\ \mathrm{ds_j})^{-0.5} \tag{5}$$

where M is the number of edges in G, μ is the cyclomatic number of G and ds_i (i = 1, 2, ..., N; N is number of vertices in G) is a distance sum.

The distance sum for a vertex i (ds_i) represents the sum of all entries in the corresponding row (or column) of the distance matrix $\boldsymbol{D}$:

$$\mathrm{ds_i} = \sum_{j=1}^{N} (D)_{ij} \tag{6}$$

The cyclomatic number μ of a polycyclic graph G is equal to the minimum number of edges necessary to be erased from G in order to transform it into the related acyclic subgraph:

$$\mu = M - N + 1 \tag{7}$$

A procedure to compute the Balaban index for heterosystems has been suggested by Barysz *et al.*[17] These authors have modified the elements of the distance matrix for heterosystems as follows:

a) The diagonal elements

$$(D)_{ii} = 1 - (Z_c / Z_i) \tag{8}$$

where Z_c = 6 and Z_i is the atomic number of the given element;

b) The off-diagonal elements

$$(D)_{ij} = \sum_r k_r \tag{9}$$

where the summation is over all bonds. The bond parameter k_r is given by:

$$k_r = (1/b_r)\ (Z_c^2/\ Z_i Z_j) \tag{10}$$

where b_r is the bond weight with the following values: 1 for single bond, 2 for double bond. The values of $(D)_{ij}$ for various heteroatoms and k_r for various types of heterobonds are given in the literature.[9,17]

The Information-Theoretic Index, I(G)

The information-theoretic index I(G) was calculated by the application of information-theoretic formalism on chemical graph, by means of the total information content or by modification of Shannon's relation.[25,26]

$$I(\mathrm{G}) = -\sum_{i=1}^{n} \frac{2N_1}{N\,(N-1)} \log_2 \frac{2N_1}{N\,(N-1)} \tag{11}$$

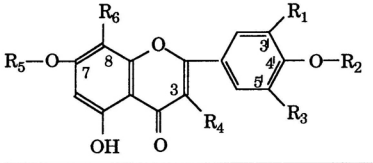
where n is the number of different sets of elements, N_i is the number of elements in the i-th set of elements and the sum is over all sets of elements. The logarithm is taken on the basis of 2 for measuring the information content in bits. A certain distance of a value i $(1 \le i \le N-1)$ appears $2N_i$ times in the distance matrix. Since the distance matrix is the symmetric matrix, the upper-triangle part of its numbers preserves all the information concerning the observed system. The total number of elements in the upper-triangle of distance matrix is $N(N-1)/2$.

RESULTS AND DISCUSSION

The statistical procedure used to derive QSAR models is the linear regression analysis, and can be either single or multivariable, depending on the number of structural descriptors used in a particular analysis.[8,9]

TABLE I

Structures of the studied flavonoids



Flavonoid number	Name of the flavonoid	R_1	R2	R3	R4	R5	R6
1	quercetin	OH	H	H	OH	H	H
2*	isoquercitrin	OH	H	H	*O*-glucose	H	H
3	hyperoside	OH	H	H	*O*-galactose	H	H
4	quercitrin	OH	H	H	*O*-rhamnose	H	H
5*	rutin	OH	H	H	*O*-glucose-rhamnose	H	H
6*	quercetin-3-*O*-rhamnoglucoside-7-*O*-rhamnoside	OH	H	H	*O*-glucose-rhamnose	rhamnose	H
7*	quercetin-3-*O*-rhamnoglucoside-4'-*O*-glucoside	OH	glucose	H	*O*-glucose-rhamnose	H	H
8	kaempferol	H	H	H	OH	H	H
9	astragalin	H	H	H	*O*-glucose	H	H
10*	kaempferol-3-*O*-rhamnoglucoside-7-*O*-rhamnoside	H	H	H	*O*-glucose-rhamnose	rhamnose	H
11	myricetin	OH	H	OH	OH	H	H
12	apigenin	H	H	H	H	H	H
13	luteolin	OH	H	H	H	H	H
14	vitexin	H	H	H	H	H	glucose
15*	scoparin-7-*O*-rhamnoglucoside	OCH_3	H	H	H	glucose-rhamnose	H

* Flavonoid glycosides isolated from *Paliurus spina-christi* Mill.

We have investigated linear, several nonlinear (such as exponential, logarithmic, quadratic, parabolic, and higher-order polynomials), and multivariate relationships between the topological indices discussed in the previous section and selected properties of flavonoids. To test the quality and accuracy of derived models, the following statistical parameters should be used: n is the number of data points, r the correlation coefficient, s the standard deviation and F is the F-ratio between the variances of observed and calculated values.

The full names and structures of flavonoid glycosides isolated from the leaves of *Paliurus spina-christi* Mill. and related compounds studied are depicted in Table I.

Table II shows the selected physicochemical properties (molecular weight, M.w., melting point, M.p., van der Waals volume, V_w) partition coefficient, log P (calculated using Rekker's method) and topological indices (Wiener index, W, valence connectivity index, χ^v, Balaban index, J, information theoretic index, I, and the number of vertices, N) for studied compounds. The total number of vertices, N, in the molecular graph was considered a topological parameter. It is identical to the number of atoms in the hydrogen-depleted molecular structure.

TABLE II

The selected physicochemical properties (molecular weight, M.w. and melting point, M.p.) partition coefficient, log P (o/w), calculated according to Rekker's method, van der Waals-volume, V_w, number of vertices, N, and topological indices (Wiener index, W(G), information-theoretical index, I(G), Balaban index, J(G), and valence connectivity index, χ^v(G)) of the studies flavonoids

Flavonoid	M.w. g mol^{-1}	M.p. °C	log P	$V_w \cdot 10^2$ Å^3	N	W(G)	I(G)	J(G)	χ^v(G)
1	302.23	314.0	–2.966	2.298	22	1253	3.42	2.35	6.03
2	464.37	234.0	–8.976	3.484	33	3423	3.63	2.07	9.47
3	464.37	237.0	–8.976	3.484	33	3423	3.63	2.07	9.47
4	448.37	183.0	–7.313	3.395	32	3164	3.60	2.07	9.35
5	610.51	189.0	–13.243	4.602	43	7145	4.02	1.68	12.79
6	756.65	199.0	–18.658	5.720	53	12534	4.27	1.47	16.34
7	772.65	–	–20.321	5.788	54	13943	4.37	1.49	16.24
8	286.23	276.0	–2.446	2.230	21	1109	3.39	2.33	5.90
9	448.37	178.0	–8.376	3.416	32	3155	3.61	2.05	9.35
10	740.65	–	–18.058	5.571	52	12287	4.28	1.50	15.99
11	318.23	353.0	–3.55	2.366	23	1401	3.43	2.38	6.15
12	270.23	347.0	–0.92	2.161	20	1005	3.41	2.23	5.78
13	286.23	329.0	–1.52	2.230	21	1141	3.43	2.25	5.89
14	434.39	260.0	–6.795	3.335	31	2828	3.57	2.01	9.19
15	608.54	–	–14.062	4.701	43	7904	4.25	1.54	13.08

Below we list models which produced the best statistical characteristic for each considered property.

1. Molecular weight (M.w.)

$$\text{M.w.} = 24.802\ (\pm 7.164) + 45.292\ (\pm 0.666) \cdot \chi^{v} \qquad (12)$$

$$n = 15 \quad r = 0.999 \quad s = 9.793 \quad F = 4628.038$$

A plot of molecular weight, M.w., *vs.* valence connectivity index, χ^{v}, is given in Figure 1.

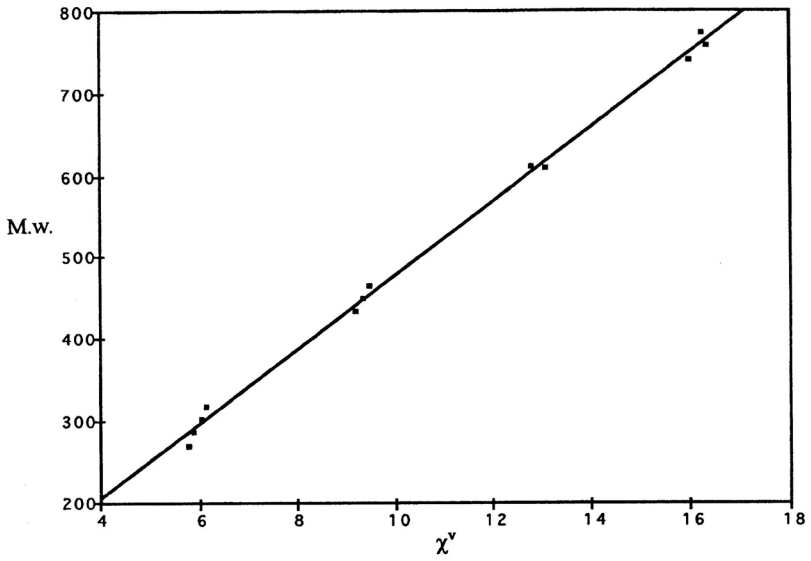


Figure 1. The linear QSPR model of molecular weight, M.w. of flavonoid glycosides isolated from *Paliurus spina-christi* Mill., based on the valence connectivity index, χ^{v}.

2. Melting point (M.p.)

$$\text{M.p.} = 646.024\ (\pm 85.811) - 69.862\ (\pm 17.764) \cdot \chi^{v} + 2.611\ (\pm 0.839) \cdot (\chi^{v})^{2} \qquad (13)$$

$$n = 12 \quad r = 0.894 \quad s = 32.384 \quad F = 17.862$$

A plot of melting point, M.p., *vs.* valence connectivity index, χ^{v}, is given in Figure 2.

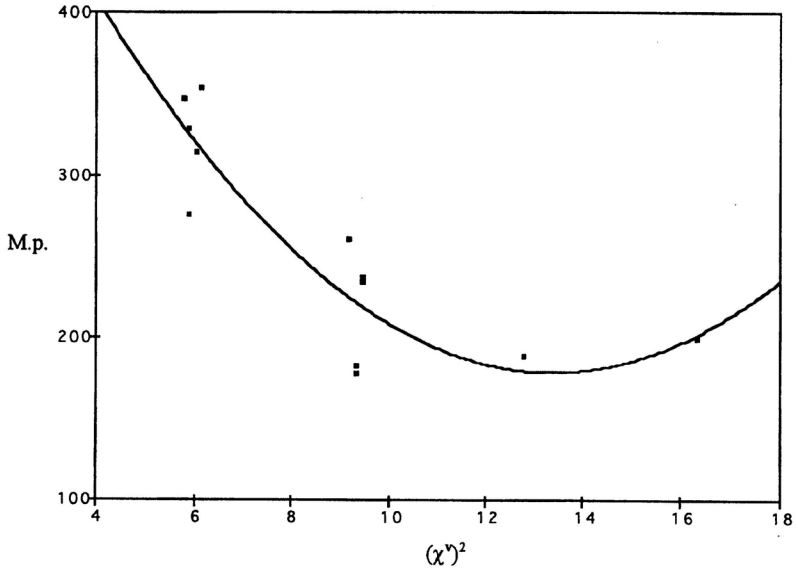


Figure 2. The parabolic QSPR model of melting point, M.p. of flavonoid glycosides isolated from *Paliurus spina-christi* Mill., based on the valence connectivity index, χ^v.

3. Van der Waals volume (V_w)

$$V_w = 0.259\ (\pm 0.029) + 0.337\ (\pm 0.003) \cdot \chi^v \qquad (14)$$

$$n = 15 \quad r = 0.999 \quad s = 0.039 \quad F = 15809.087$$

A plot of van der Waals volume, V_w, *vs.* valence connectivity index, χ^v, is given in Figure 3.

4. Partition coefficient, log P

$$\log P = 7.362\ (\pm 0.\ 577) - 1.633\ (\pm 0.054)\ \chi^v \qquad (15)$$

$$n = 15 \quad r = 0.993 \quad s = 0.789 \quad F = 926.046$$

A plot of partition coefficient, log P, *vs.* valence connectivity index, χ^v, is given in Figure 4.

Many of the correlations observed among the physical properties examined are expected from fundamental consideration. The majority of properties considered are constitutive, *i.e.* shape-dependent properties, determined by the strength of intermolecular forces[27]. This is evident for the highly correlated melting point. However, the molecular weight and molar volume are

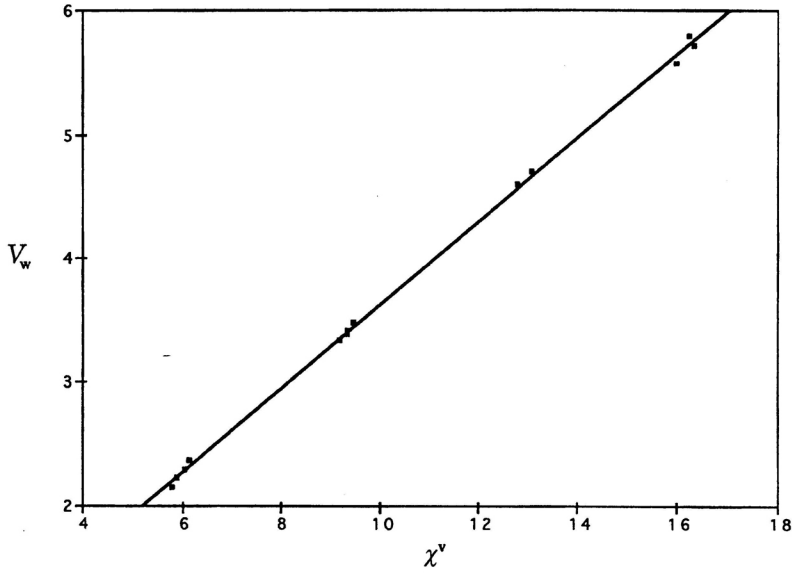


Figure 3. The linear QSPR model of van der Waals volume, V_w of flavonoid glycosides isolated from *Paliurus spina-christi* Mill., based on the valence connectivity index, χ^v.

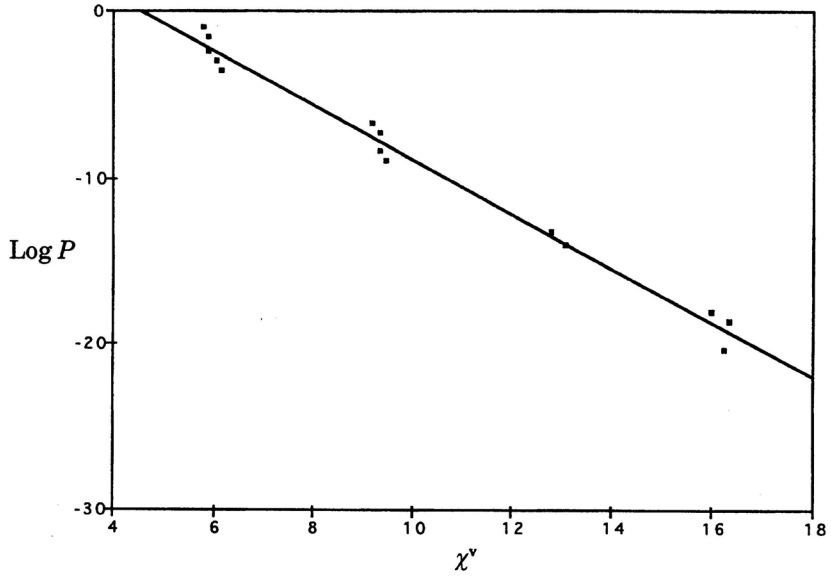


Figure 4. The linear QSPR model of partition coefficient, log P of flavonoid glycosides isolated from *Paliurus spina-christi* Mill., based on the valence connectivity index, χ^v.

additive properties which, to a good approximation, can be expressed as sums of atomic or bond contributions. Lipophilicity is the property of a molecule which depends on and can be changed by modifications in molecular structure.[28] The partition of drugs between n-octanol/water reflects the process by which drugs are distributed between the aqueous exobiophase and the lipophilic biophase. Interest in the use of hydrophobic parameters to rationalize interactions of small ligands with various macromolecules in the field of biochemistry, medicinal chemistry and environmental science is continously increasing.[29] A number of empirical and theoretical approaches have been developed during the last twenty years for calculation of log P values.[30–33] Table II shows the small values of log P which are all negative for the investigated compounds, which indicates a decrease of lipophilicity.

The QSPR models based on the valence connectivity index have shown the best correlation (r = 0.99) with specific physical parameters (especially with molecular weight and lipophilicity) of the studied flavonoids. Other examined indices and multiple regression analysis have also shown good results (r = 0.91–0.97).

In this paper we also investigated the relationship between the van der Waals volume (V_w) and lipophilicity (log P). The van der Waals interactions play a very important role in chemistry and in the sphere of biodisciplines. All investigated flavonoids show expressive hydrophobicity. A highly significant correlation between the partition coefficient, log P, and van der Waals volume, V_w (calculated according to the method described by Moriguchi[34] *et al.*) was obtained (r = 0.99).

It may be taken that non-specific behaviour (including lipophilicity) of molecules is mainly based on their size and polarity.

A plot of partition coefficient, log P, *vs* van der Waals volume, V_w, is given in Figure 5.

$$\log P = 8.656\ (\pm 0.506) - 4.856\ (\pm 0.131) V_w \qquad (16)$$

$$n = 15 \quad r = 0.995 \quad s = 0.649 \quad F = 1377.176$$

The results obtained here have encouraged us to undertake the QSAR study of flavonoid glycosides of *Paliurus spina-christi* Mill.

CONCLUDING REMARKS

In this paper, we give QSPR models based on topological indices and lipophilicity for flavonoid glycosides isolated from the leaves of the plant *Paliurus spina-christi* Mill. and for some related flavonoids. Flavonoids have various biological effects. They are very common in nature, mainly in food of plant origin for humans and animals.

Here, we give a preliminary study for the future QSAR investigation. It should be pointed out that the physicochemical properties of flavonoids determine their biological action. It is known that only those chemicals which interact with a particular transport system can be introduced into biological world. For this reason, special emphasis is to be laid on lipophilicity of flavonoids. Of the topological indices, the valence connectivity indices have been most extensively tested in the study of lipophilicity.[27,29]

The best models of examined physicochemical properties are based on linear or polynomial regression with the valence connectivity index.

These results may be related to the ability of the connectivity index to model the shape of flavonoid molecules. The Balaban index, which is in fact a variant of the connectivity index, is also a good descriptor for the shape of the molecules.

In conclusion, the van der Waals volume as well as lipophilicity are useful parameters for structure-activity analysis and especially for designing drugs because these parameters can be easily calculated for a wide variety of molecules.

The practical value of these models is in the predicting properties and activity of yet unknown flavonoids. Our future study will try to make clear whether the activity of flavonoids depends on the following statements: a) glycosides are much less effective than the corresponding aglycons; b) the presence of the C_2, C_3 double bond is essential; c) a high number of OH group can decrease activity.

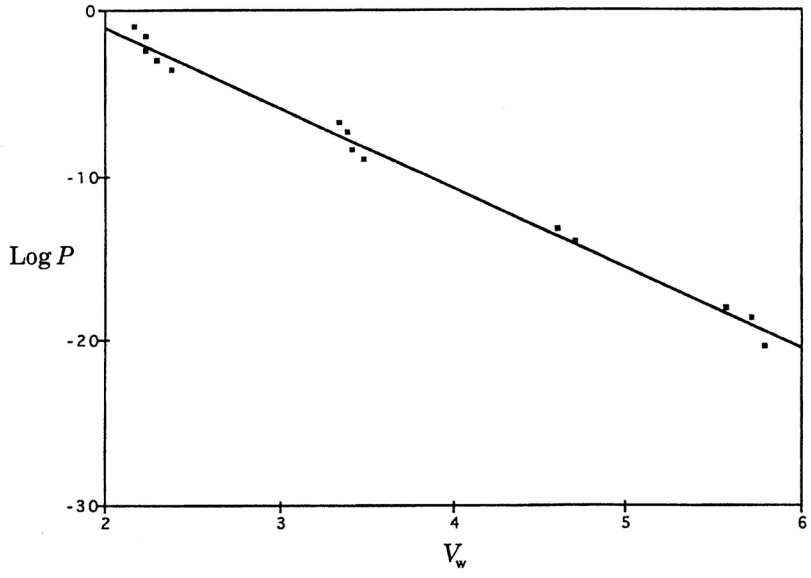


Figure 5. A plot of partition coefficient, log P, against van der Waals volume, V_w for the flavonoid glycosides isolated from *Paliurus spina-christi* Mill.

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SAŽETAK

Kvantitativno modeliranje flavonoidnih glikozida izoliranih iz drače, *Paliurus spina-christi* Mill.

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Predloženo je nekoliko QSPR modela za predviđanje svojstava flavonoidnih glikozida izoliranih iz drače (*Paliurus spina-christi* Mill.) i nekih srodnih flavonoida. Lipofilnost, log P, za sve ispitane flavonoide izračunana je metodom prema Rekkeru. Značajne korelacije dobivene su između lipofilnosti i van der Waalsova volumena, što upućuje na nespecifično ponašanje molekula, koje se temelji na njihovoj veličini i polarnosti.

Topologijski indeksi uporabljeni u korelacijskoj analizi uključuju Wienerov broj, W(G), indeks valencijske povezanosti, χ^{v}(G), Balabanov indeks, J(G), i informacijsko-teorijski indeks, I(G).

Najbolji modeli za istraživane flavonoide dobiveni su s indeksom valencijske povezanosti.