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Chapter 4

QSRP Prediction of Retention Times of Chlorogenic Acids in Coffee by Bioplastic Evolution

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Additional information is available at the end of the chapter

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Abstract

Caffeoyl-, feruloyl- and dicaffeoylquinic (chlorogenic) acids in infusions from green and medium roasted coffee beans were identified and quantified by reverse phase liquid chromatography. The chromatographic retention times of chlorogenic acids in coffee are modeled by structure-property relationships. Bioplastic evolution is a view in evolution that conjugates the result of acquired features, and relationships that come out between the principles of evolutionary indeterminacy, morphological determination, and natural selection. Here, it is used to invent the coordination index, which is utilized to typify chlorogenic acids chromatographic retention times. The factors utilized to compute the co-ordination index are the standard molar formation enthalpy, molecular bare, and hydrophobic solvent-accessible surface areas, as well as fractal dimensions. The morphological and coordination indices provide strong correlations. Effect of different types of features is analyzed: thermodynamic, geometric, fractal, etc. Properties are molar formation enthalpy, bare molecular surface area, etc., in linear correlation models. Formation enthalpy, etc. distinguish chlorogenic acids molecular structures.

Keywords: biological plastic evolution, morphological index, co-ordination index, formation enthalpy, molecular surface, hydrophobic accessible surface, fractal dimension, solvation parameter model, chlorogenic acid, hydroxycinnamate, coffee, *Coffea*

1. Introduction

Coffee terpenoids, cafestol, kaweol and 16-*O*-methylcafestol, which occur as fatty acid (FA) esters (FAEs), are responsible for the reversible rise in plasma low-density lipoprotein (LDL) cholesterol (CHOL) observed in some populations (*e.g.*, Scandinavia, Italy) [1–3]. High consumption of boiled, unfiltered coffee was linked to risen levels of homocysteine [4, 5], which, along with risen CHOL, is a known risk factor for cardiovascular disease (CVD). Freshly brewed and instant

coffee can induce mutagenic cytotoxic effects *in vitro* [6, 7], because of the gradual formation of hydrogen peroxide H_2O_2 in the beverage [8], which is a reactive oxygen species (ROS) capable of damaging biomolecules and membranes [9]. However, a 5.5% rise in plasma antioxidant activity (AOA) was observed in human volunteers after a single intake of brewed coffee, suggesting its *in vivo* AOA [10].

Coffee contains chlorogenic acids (CGAs) with the amounts varying between green (GCBs) and roasted (RCBs) coffee beans [11, 12]. *Via* an LDL oxidation assay, phenolic compounds in coffee showed AOA, which levels varied depending on coffee beans source and roasting degree [13]. 5-*O*-Caffeoylquinic acid (5-CQA) presented anticarcinogenic properties [14, 15] and a protective role *vs*. LDL oxidation in an *ex vivo* animal model [16]. It and other hydroxycinnamates protected *vs*. the oxidation of human LDL particles *in vitro* [17–20], a process playing a role in atherosclerotic-plaques formation and CVD onset. Crozier and co-workers reported on-line high-performance liquid chromatography (HPLC) analysis of phenolic compounds AOA in brewed, paper-filtered coffee [21]. Antioxidant activity and principles of Vietnam bitter tea *Ilex kudingcha* were informed [22]. Purification and HPLC analysis of CQAs from Kudingcha made from *I. kudingcha* were published [23]. Simultaneous qualitation and quantitation of CGAs in Kuding tea were reported *via* ultra-HPLC-diode array detection coupled with linear ion trap-Orbitrap mass spectrometer (UHPLC-DAD-LTQ-Orbitrap-MS) [24]. Preparation, phytochemical investigation and safety evaluation of CGA products were informed from *Eupatorium adenophorum* [25].

The model used in this work is an extension of solvent-dependent conformational analysis program (SCAP) octanol-water model to organic solvents [26]. In earlier publications, SCAP was applied for partition coefficients of porphyrins, phthalocyanines, benzobisthiazoles, fullerenes, acetanilides, local anesthetics [27], lysozyme [28], barbiturates, hydrocarbons [29], polystyrene [30], Fe–S proteins [31], C-nanotubes [32] and D-glucopyranoses [33]. Bioplastic evolution was applied to phenylalcohols, 4-alkylanilines [34], valence-isoelectronic series of aromatics [35], phenylurea herbicides [36, 37], pesticides [38, 39], methylxanthines and cotinine [40, 41]. Quantitative structure-activity/property relationships (QSARs/QSPRs) were applied to isoflavonoids [42] and sesquiterpene lactones [43]. Mucoadhesive polymer hyaluronan, as biodegradable cationic and zwitterionic-drug delivery vehicle, favors transdermal penetration absorption of caffeine (Caff) [44, 45]. The present report describes QSPR analysis and estimation of CGAs chromatographic retention times. The goal of the study is to identify the properties that differentiate CGAs consistent with chromatographic retention times. The work uses the chemical index in CGAs. The aim of this research is the corroboration of the value of the index by its ability to distinguish CGAs, as well as its concern as a prognostic descriptor for retention time evaluated with regard to molar formation enthalpy, molecular bare, and hydrophobic solvent-accessible surface areas, and fractal dimensions. Section2 describes the computational method. Sections3 and 4 illustrate and discuss the calculation results. Finally, Section5 summarizes our conclusions.

2. Computational method

Biological plastic (bioplastic) evolution is a perspective of the process of the evolution of species. It conjugates the result of (1) the acquired characters and (2) relationships between

the principles of evolutionary indeterminacy, morphological determination and natural selection in evolutionary biology. The relationship between morphology and functionality in organisms is that morphology is the substance prop of functionality, which is the dynamic result of the former in the circumstance of the interaction between physical environment and living matter. Morphology, functionality, energy outlay and vital viability are equally affected: When a morphology is functional, it accomplishes its work with minimum energy outlay, and the vital viability of the organ or organism is maximum. Counting these ideas includes defining the *functional coordination index* I_c, which is expressed as the relation between the work achieved by morphology T and the characteristic *morphological index* I_m, consistent with:

$$I_c = \frac{T}{I_m} \tag{1}$$

The larger the work T attained by a specific morphology I_m, the larger the I_c. For an organism, I_m was suggested as the relation between the morphological surface area S and body mass W [46]:

$$I_m = \frac{S}{W} \tag{2}$$

The substitution of Eq. (2) in (1) turns out to be:

$$I_c = \frac{W \cdot T}{S} \tag{3}$$

where T is given by its correspondence in classical mechanics:

$$T = W \cdot x \frac{d^2x}{dt^2} \tag{4}$$

Substituting Eq. (4) in (3), it turns out to be:

$$I_c = \frac{W^2 \cdot x}{S} \frac{d^2x}{dt^2} \tag{5}$$

The I_c rises with the following settings: (1) the larger the body mass at equivalent journeyed time or distance, the larger the I_c; (2) the I_c is proportional to the distance journeyed in the smallest achievable period; (3) the lesser body surface area, the larger I_c and the co-ordination between function and morphology needs lesser energy outlay.

Code SCAP is founded on a representation by Hopfinger, parametrized for 1-octanol-water solvents [47]. The conjecture is that one is able to center a *solvation sphere* on all functional groups in the molecule [48]. The overlapping volume V° between the solvation sphere and van der Waals (VdW) spheres of the resting atoms is computed. Code SCAP handles factors for a solvent: (1) n: maximal number of solvent molecules satisfying the solvation sphere; (2) Δg°: change of Gibbs free energy linked with the removal of one molecule of solvent out of the solvation sphere [49, 50]; (3) R_v: radius of the solvation sphere; (4) V_f: free volume accessible for a solvent molecule in the solvation sphere [51]. In the solvation sphere, a fraction of its volume

keeps out solvent molecules. The volume is made of VdW volume of the functional group at which the sphere is centered and a volume standing for functional groups connected to the central one. This volume is symbolized by a set of cylinders. The difference between the total volume of the solvation sphere and that prohibited for the solvent molecules stands for the volume V' that is accessible for n solvent molecules. The V_f is computed by $V_f = V'/n–V_s$. The variation of free energy linked to the removal of every solvent molecule out of the solvation sphere of a functional group R turns out to be: $\Delta G_R^\circ = n\Delta g^\circ(1–V^\circ/V')$, and the free energy of solvation of molecule results: $\Delta G_{solv}^\circ = –\Sigma_{R=1}^{N}\Delta G_R^\circ$. The 1-octanol-water partition coefficient P results:

$$RT\ \ln P = \Delta G^o_{solv}(\text{water}) - \Delta G^o_{solv}(1-\text{octanol}) \tag{6}$$

at a certain temperature T got as 298K, where R is the gas constant, and ΔG_{solv}°(1-octanol) and ΔG_{solv}°(water), in kJ·mol^{-1}, are the standard-state Gibbs solvation free energies. Extending SCAP for other solvents, the 1-octanol factors were customized considering the result of solvent permittivity and molecular volume. For a general solvent, the maximal number of solvent molecules permitted packing the solvation sphere is connected to the molecular volume of the solvent by:

$$n_s = n_o\left(\frac{V_s}{V_o}\right)^{\frac{\log\frac{n_o}{n_w}}{\log\frac{V_o}{V_w}}} \tag{7}$$

where V_o, V_w and V_s are the molecular volumes of 1-octanol, water and the general solvent. The n_o, n_w and n_s are the maximal numbers of molecules of 1-octanol, water, and the general solvent allowed packing the solvation sphere. The change in the standard Gibbs free energy connected to the removal of one molecule of solvent out of the solvation sphere, Δg_s°, is computed *via* the extended Born equation:

$$\Delta g^o_s = \Delta g^o_o \frac{1-\frac{1}{\varepsilon_s}}{1-\frac{1}{\varepsilon_o}} = \Delta g^o_o \frac{\varepsilon_o(\varepsilon_s-1)}{\varepsilon_s(\varepsilon_o-1)} \tag{8}$$

where Δg_s° is Δg° for 1-octanol, and ε_o and ε_s are the permittivities of 1-octanol and the general solvent. The radius of the solvation sphere results connected to the molecular volume of the solvent molecule by:

$$R_{v,s} = R_{v,o}\left(\frac{V_s}{V_o}\right)^{\frac{1}{3}} \tag{9}$$

where $R_{v,o}$ is R_v in 1-octanol. The free volume accessible for a solvent molecule in the solvation sphere is:

$$V_{f,s} = V_{f,o}\frac{V_s}{V_o} \tag{10}$$

where $V_{f,o}$ is V_f in 1-octanol.

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The models were obtained *via* multiple linear regression (MLR). Correlation coefficient *r* was used as the calibration function of the regression models, together with standard deviation *s*, variance ratio *F*, prediction error sum of squares (PESS), mean absolute percentage error (MAPE) and approximation error variance (AEV). Statistics *r*, *s* and *F* were calculated with Microsoft Excel 2016, and PESS, MAPE and AEV, with Knowledge Miner for Excel. Our codes SCAP and TOPO [52] are available from the authors at the Internet (torrens@uv.es) and are free for academics.

3. Calculation results

For nine CGAs, *viz*. 3/4/5-*O*-caffeoyl- (CQAs), 3/4/5-*O*-feruloyl- (FQAs) and 3, 4/3, 5/4, 5-*O*-dicaffeoylquinic (diCQAs) acids (*cf*. **Figure 1**), reverse phase (RP) HPLC retention times R_t were taken from Crozier and co-workers.

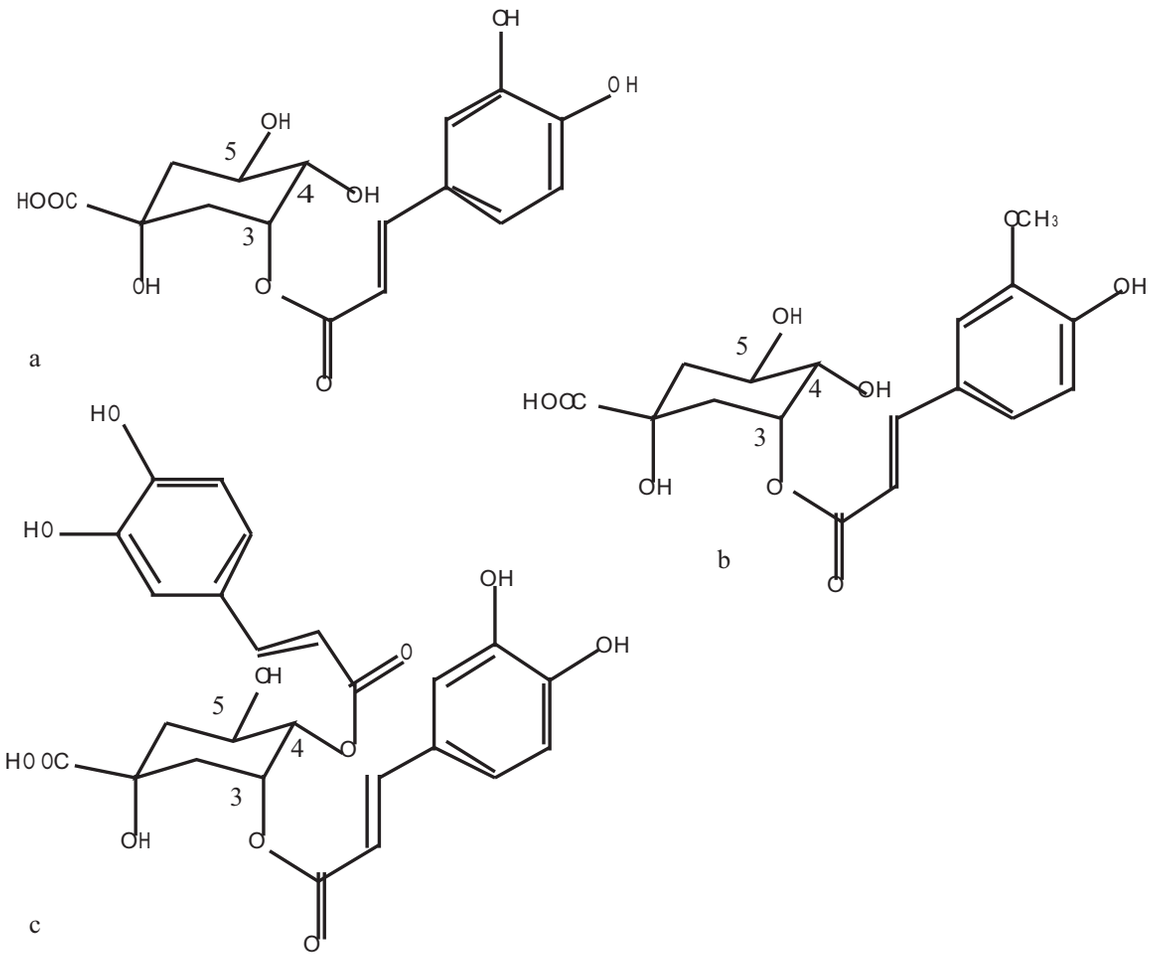

Figure 1. Structures: (a) 3-*O*-caffeoylquinic; (b) 3-*O*-feruloylquinic; (c) 3,4-*O*-dicaffeoylquinic acids.

The 3-CQA was taken as *reference* retention time R_t° because of least R_t (*cf*. **Table 1**). Ratios $(R_t\text{-}R_t^\circ)/R_t^\circ$ were calculated. Standard molar formation enthalpy was computed with code MOPAC-AM1 [53]. Molecular bare *S* and hydrophobic solvent (water)-accessible (HBAS) surface areas, fractal dimension *D* and this averaged for non-buried atoms *D′* were calculated with our code TOPO.

The use of the co-ordination index in the chemical description of molecules needs to change variables *T*, *S* and *W* [Eq. (3)]: *T* is redescribed as minus the standard molar formation enthalpy ($kJ{\cdot}mol^{-1}$), *S* is the molecular surface area ($Å^2$), and *W* is the molecular mass ($g{\cdot}mol^{-1}$). Chemical indices for CGAs characterization (*cf*. **Table 2**) show that I_m remains constant, while I_c rises with *W*.

Indices variation for CGAs *vs*. molecular weight *W* (*cf*. **Figure 2**) shows that most points collapse for CQAs, FQAs and diCQAs, every group with three isomers. The only descriptor that remains almost constant is I_m. Descriptors more sensitive to *W* decay: $I_c > T > S > I_m$.

Variations of $(R_t\text{-}R_t^\circ)/R_t^\circ$ *vs*. morphological index I_m show fit; the regression turns out to be:

$$\frac{R_t - R_t^o}{R_t^o} = 43.7 - 45.3I_m \tag{11}$$

$n = 9$, $r = 0.808$, $s = 1.047$, $F = 13.2$.

PESS = 0.3972, MAPE = 36.39%, AEV = 0.3472.

Molecule	R_t (min)	$R_t\text{-}R_t^\circ$ (min)	$(R_t\text{-}R_t^\circ)/R_t^\circ$	ΔH_f° ($kJ{\cdot}mol^{-1}$)[a]	HBAS ($Å^2$)[b]	D[c]	D'[d]
1. 3-*O*-Caffeoylquinic acid (3-CQA)	9.0	0.0	0.000	−1545.4	218.42	1.390	1.480
2. 4-*O*-Caffeoylquinic acid (4-CQA)	13.6	4.6	0.511	−1550.0	241.44	1.375	1.498
3. 5-*O*-Caffeoylquinic acid (5-CQA)	15.4	6.4	0.711	−1570.5	238.38	1.387	1.458
4. 3-*O*-Feruloylquinic acid (3-FQA)	16.2	7.2	0.800	−1519.5	281.61	1.410	1.490
5. 4-*O*-Feruloylquinic acid (4-FQA)	23.6	14.6	1.622	−1524.2	305.78	1.383	1.511
6. 5-*O*-Feruloylquinic acid (5-FQA)	27.3	18.3	2.033	−1541.4	301.12	1.395	1.476
7. 3,4-*O*-Dicaffeoylquinic acid (3,4-diCQA)	41.9	32.9	3.656	−1839.7	296.65	1.445	1.534
8. 3,5-*O*-Dicaffeoylquinic acid (3,5-diCQA)	44.7	35.7	3.967	−1865.2	322.59	1.453	1.562
9. 4,5-*O*-Dicaffeoylquinic acid (4,5-diCQA)	49.1	40.1	4.456	−1867.2	308.05	1.434	1.500

[a]Standard molar formation enthalpy calculated with MOPAC-AM1.
[b]HBAS: hydrophobic water-accessible surface area.
[c]*D*: molecular fractal dimension.
[d]*D′*: molecular fractal dimension averaged for non-buried atoms.

Table 1. Retention time, formation enthalpy and fractal dimensions for chlorogenic acids.

Molecule	W (g·mol^{-1})[a]	T (kJ·mol^{-1})[b]	S (Å^2)[c]	I_m (mol·Å^2·g^{-1})[d]	I_c (kJ·g·mol^{-2}·Å^{-2})[e]
3-*O*-Caffeoylquinic acid	354	1545.4	328.77	0.929	1664.0
4-*O*-Caffeoylquinic acid	354	1550.0	329.08	0.930	1667.4
5-*O*-Caffeoylquinic acid	354	1570.5	335.65	0.948	1656.4
3-*O*-Feruloylquinic acid	368	1519.5	345.85	0.940	1616.8
4-*O*-Feruloylquinic acid	368	1524.2	346.24	0.941	1620.0
5-*O*-Feruloylquinic acid	368	1541.4	351.14	0.954	1615.4
3,4-*O*-Dicaffeoylquinic acid	516	1839.7	459.17	0.890	2067.4
3,5-*O*-Dicaffeoylquinic acid	516	1865.2	464.60	0.900	2071.6
4,5-*O*-Dicaffeoylquinic acid	516	1867.2	447.14	0.867	2154.8

[a]*W*: molecular weight (g·mol^{-1}).
[b]*T*: minus standard formation enthalpy (kJ·mol^{-1}).
[c]*S*: molecular surface area (Å^2).
[d]I_m: morphological index (mol·Å^2·g^{-1}).
[e]I_c: co-ordination index (kJ·g·mol^{-2}·Å^{-2}).

Table 2. Bioplastic evolution indices for chlorogenic acids.

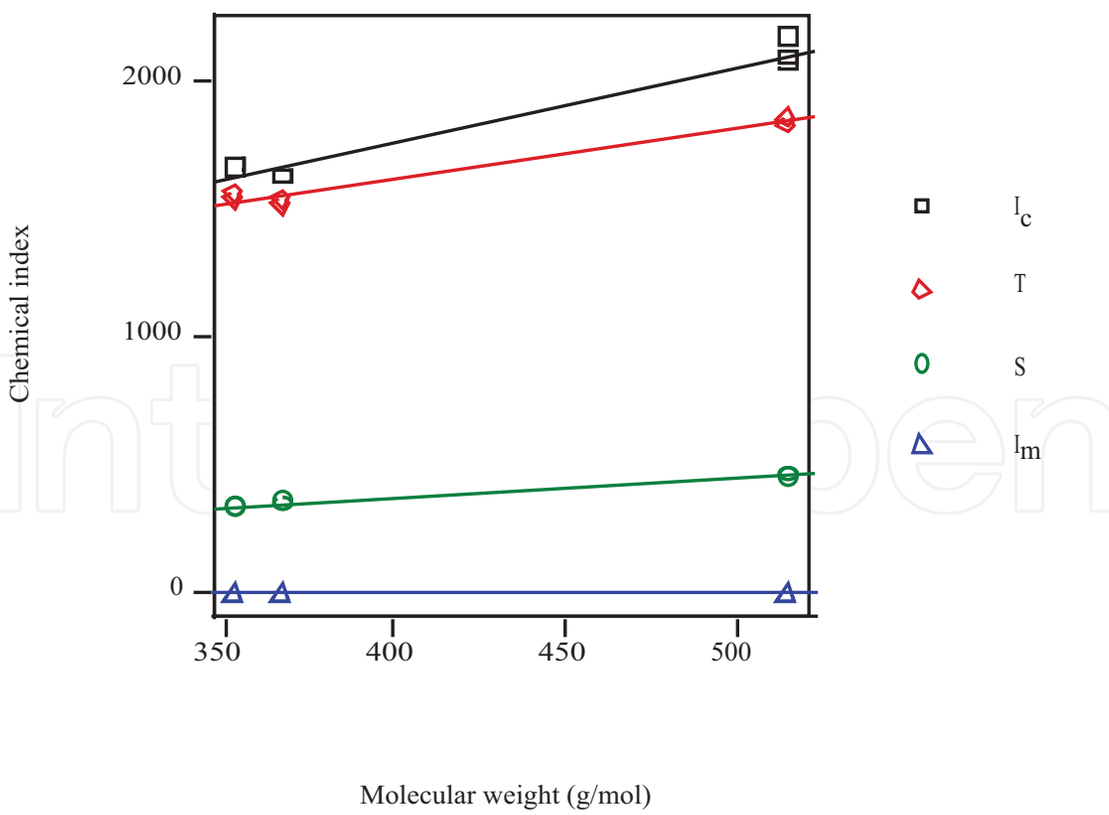

Figure 2. Variation of chemical indices for CGAs *vs*. molecular weight: $y = 589+2.92x$; $y = 817+2.01x$; $y = 64.7+0.761x$; $y=1.07–0.000346x$.

where MAPE is 36.39% and AEV, 0.3472. The use of coordination index I_c improves the model:

$$\frac{R_t - R_t^o}{R_t^o} = -9.70 + 0.00651 I_c \tag{12}$$

$n = 9$, $r = 0.906$, $s = 0.754$, $F = 31.9$.

PESS = 0.2038, MAPE = 25.80%, AEV = 0.1800.

and AEV decays by 48%. The utilization of the standard molar formation enthalpy betters the fit:

$$\frac{R_t - R_t^o}{R_t^o} = -13.8 - 0.00959 \Delta H_f^o \tag{13}$$

$n = 9$, $r = 0.916$, $s = 0.714$, $F = 36.3$.

PESS = 0.1857, MAPE = 26.15%, AEV = 0.1616.

and AEV drops by 53%. The application of the bare molecular surface area S improves the model:

$$\frac{R_t - R_t^o}{R_t^o} = -8.09 + 0.0266 S \tag{14}$$

$n = 9$, $r = 0.950$, $s = 0.556$, $F = 64.5$.

PESS = 0.1232, MAPE = 22.11%, AEV = 0.0979.

and AEV decreases by 72%.

The inclusion of the hydrophobic solvent (water)-accessible surface area HBAS improves the fit:

$$\frac{R_t - R_t^o}{R_t^o} = -12.3 + 0.00472 I_c + 0.0210 \text{HBAS} \tag{15}$$

$n = 9$, $r = 0.988$, $s = 0.291$, $F = 127.5$.

PESS = 0.0365, MAPE = 9.86%, AEV = 0.0230.

and AEV decays by 93%. The fractal dimension averaged for *non-buried* atoms D' betters the fit:

$$\frac{R_t - R_t^o}{R_t^o} = -2.57 - 0.00801 \Delta H_f^o + 0.0229 \text{HBAS} - 10.0 D' \tag{16}$$

$n = 9$, $r = 0.995$, $s = 0.204$, $F = 174.7$.

PESS = 0.0141, MAPE = 6.63%, AEV = 0.0095.

and AEV decreases by 97%. The incorporation of the fractal dimension D improves the model:

$$\frac{R_t - R_t^o}{R_t^o} = 7.86 - 0.00899\Delta H_f^o + 0.0257\text{HBAS} - 7.80D - 11.3D' \quad (17)$$

$n = 9$, $r = 0.998$, $s = 0.154$, $F = 232.2$.

PESS = 0.0091, MAPE = 5.16%, AEV = 0.0058.

and AEV drops by 98%. The inclusion of the bare molecular surface area S betters the correlation:

$$\frac{R_t - R_t^o}{R_t^o} = 11.0 - 0.00776\Delta H_f^o + 0.00606S + 0.0222\text{HBAS} - 11.2D - 9.71D' \quad (18)$$

$n = 9$, $r = 0.999$, $s = 0.136$, $F = 239.1$.

PESS = 0.0060, MAPE = 4.00%, AEV = 0.0038.

and AEV decays by 99%. The best non-linear models do not improve the correlation. Additional fitting parameters were tested: molecular dipole moment, weight, volume, globularity, rugosity, hydrophilic and total solvent-accessible surfaces, accessibility and fractal dimension for external atoms minus fractal index (D'–D). Notwithstanding, the results do not improve Eqs. (12)–(18).

4. Discussion

Food effects on health rightly worry consumers. Mass media tend to satisfy the permanent question, and physicians must face many queries from the persons that come to consult them. Information sources are scattered in many scientific journals, and a few domains exist that be so dispersed in different databases international journals. Information circulates badly, critical syntheses are rare, and an important passivity exists in knowledge transmission. Because of the great interest devoted to their health, consumers are receptive to all new accounts that concern food. Mass media know it and reply in a simplified way *via* all new data, where the impact will be proportional to novelty character. Results of scientific studies must be interpreted *vs*. experimental conditions, transmitting them without nuance finish in a misinformation and myths creation. Cafés popularization during the nineteenth century, replacing beer bars, decreased alcohol consumption during working days, improving health and safety at work. Daily coffee is something to which many people cannot renounce. It does not matter if it is consumed to increase energy or enjoy it in the company but one thing is clear: The taste and quality are important factors. In order to guarantee the best taste and quality, many RCB companies place their trust in good-quality equipment. Many physiological properties either favorable or unfavorable to health were attributed to coffee [54]. Some are exact, some other, mistaken. Errors come from two causes: tradition and experimental results interpretation. As coffee physiological effects frequently entail by subjective observations, and their intensity is variable from one person to another, early generalizations were made, which led to definitive takings of the position that entertain public misinformation. According to some studies, to drink three or four cups of coffee per day presents positive effects for health. It is indifferent that it be decaffeinated

or not. Besides Caff and flavorings, coffee is rich in antioxidants, responsible for this be so healthy. Decaffeinated and GCBs would be more healthy than RCBs coffee. Caffeine is more concentrated in tea leaves than in GCB/RCBs. However, more caffeine exists in a coffee than in a tea drink because of the different preparation methods. Molecule Caff acts by impeding adenosine $A_{1/2A}$ receptors ($A_{1/2A}R$), pointing to that some A_1Rs are tonically more active. Mice were made with a targeted disturbance of the second coding exon of A_1R ($A_1R^{-/-}$) [55]. They raised and increased mass as normal, and presented a usual heart speed, blood pressure, and body temperature. In the majority of behavioral experiments, they resulted alike $A_1R^{+/+}$ but $A_1R^{-/-}$ mice presented signals of risen nervousness. Electrophysiological footages from pieces of the hippocampus showed that the inhibition arbitrated by adenosine and increase arbitrated by theophylline of excitatory glutamatergic neurotransmission resulted put to an end in $A_1R^{-/-}$ mice. In $A_1R^{+/-}$ mice, adenosine activity was halved, as resulted in the figure of A_1Rs. In $A_1R^{-/-}$ mice, the painkilling consequence of intrathecal adenosine resulted misplaced, and thermal hyperalgesia was shown, but morphine painkilling result was whole. The decay of neuronal potency on hypoxia decreased in pieces of the hippocampus and brainstem, and working revival after hypoxia decreased. The A_1Rs do not perform a fundamental position throughout development and, though they affect synaptic potency, they perform an additional position in usual physiology. However, beneath pathophysiological circumstances (*e.g.*, noxious incentive, O_2 lack), these receptors result significant. Coffee abuse turns people weaker. *Taking high Caff doses* per day for a long time *turns people more sensitive to pain* and hypoxias [56]. Caffeine is stimulant and counterproductive. Not all Caff effects are negative; for example, it is fine for vasodilating. When a premature newborn baby suffers from apnoeas (breath suspensions), administering him Caff improves lung functionality. Caffeine is also administered to patients suffering from asthma because it helps them to bronchodilate. However, all at moderate doses, as high Caff doses present the opposite effect. Another contradiction is that although coffee helps to digest, Caff is a gastric irritant because it increases the production of saliva, HCl, and substances that are released with gastric juices. It is counter-indicated in the case of ulcers and gastritis, but it presents a positive effect in the cases of gallstones as it reduces 40% the risk of suffering from them. In most cases, Caff is more negative than positive for health, although at small doses, which is what people normally take (*e.g.*, one cup of coffee in the morning, another after lunch), it presents beneficial effects as it acts as a stimulant. In pregnant women, Caff effect is higher and it is harder for them to eliminate it. Those born of women that during pregnancy drink a lot of coffee, in the first hours of life, present a small abstinence-syndrome symptomatology. It is because Caff causes dependence. When one does not drink coffee (if he habitually does it), he suffers from a headache, fatigue sensation, apathy, irritability, marked sleepiness, etc. Symptoms disappear when one drinks it again. Although one cannot label it as an addictive substance, it is considered doping, and high-competition athletes cannot drink it because it is considered a psychoactive substance that stimulates resistance and muscular strength. Caffeine is also present in tea, colas (*e.g.*, Coca-Cola®) and cocoa, although in the last, the quantity is derisory. The quantity of Caff that one consumes also depends on how the coffee is served, type of coffee or tea, etc.; for example, green (GT) presents 40% less Caff than black tea (BT) because the latter is oxidized (*fermented*), which makes that Caff come out easier. Maximum recommended quantity of Caff is 500 mg/day. Caffeine is a drug model because it is one of the most studied medicines. It is the world's most widely consumed psychoactive drug. Theobromine may serve as a lead

compound for novel drugs development. Analysis of Caff, its metabolites and phenolic compounds (CGAs) in foods, beverages, human plasma and urine is difficult because of the complex food, blood, and urine matrixes. Despite their progressive destruction during roasting, substantial amounts of CGAs survive to be extracted into domestic brews and instant coffee, and for many consumers, the beverage must be major dietary source of not only CGAs but also other antioxidants.

One of the important applications of QSAR/QSPR models is to fill data gaps, by predicting a given response property or activity from known molecular features, or physicochemical and physiological properties of new compounds, which might not be experimentally tested. The performance of a model should be evaluated based on predictions quality from the test and not from the training set, in order to obviate any overfitting problem. The use of phenomenological methods, for example, QSAR/QSPR, is restricted by the insufficient accuracy of final digits. A quantum-mechanical consideration of additive models showed that in most phenomenological approaches, systematic error is composed of two methodical errors: the same contribution of formally identical fragments and the inclusion of small molecules in training set. Two ways to improve models prognostic capabilities are: (1) compensation by introducing additional terms and (2) elimination of models systematic error. Building a model, Occam's razor (principle of maximal parsimony) philosophical approach should be used, that is, fit the least complex (most parsimonious) model that could correctly describe training data. The simpler the model, the better the generalization one is going to find.

A study was made of the relations between retention times obtained by RP-HPLC chromatography for a group of CGAs. *Via* multivariate linear regression, the corresponding molecular functions were obtained, which were selected based on their respective statistical parameters. Regression analysis of molecular functions showed a forecast of experimental elution sequence for CGAs. In order to predict experimental elution sequence in CGAs, 1–5-variable models were necessary in which the appearance of coordination index, morphological indicator, molar formation enthalpy, bare surface area *S*, hydrophobic water-accessible surface HBAS, *D* and *D′* reveals thermodynamic, geometric and fractal analyses importance in the studied property, allowing the use of such equations in forecasting property value. Molecular structures may be differentiated even in other phenolic compounds not included in the series, in brewed, paper-filtered coffee.

The QSPR linear models explaining the variation of chromatographic relative retention time *vs*. morphological I_m and coordination I_c indices show a negative correlation with I_m [Eq. (11)] and a positive association with I_c [Eq. (12)]. The best model is for index I_c [Eq. (12)], according to all statistics: correlation coefficient, standard deviation, variance ratio, prediction error sum of squares, mean absolute percentage error and approximation error variance.

Thermodynamic indices were tried in order to improve the model. The molar formation enthalpy negatively correlates with the relative retention time and betters the fit [Eq. (13)].

Geometric descriptors were assayed in order to improve the fit. The molecular surface positively correlates with the relative retention time and betters the model [Eq. (14)]. The inclusion of the hydrophobic accessible surface presents a positive correlation with the relative retention

time and improves the fit [Eq. (15)]. Notice that in this equation, index I_c shows a positive correlation, in agreement with Eq. (12).

Topological indices were tried in order to improve the model. The incorporation of the fractal dimension averaged for external (*non-buried*) atoms negatively correlates with the relative retention time and betters the fit [Eq. (16)]. In this equation, index ΔH_f° shows a negative correlation, in agreement with Eq. (13), and index HBAS presents positive association, in agreement with Eq. (15). The inclusion of the fractal dimension negatively correlates with the relative retention time and improves the fit [Eq. (17)]. In this equation, index ΔH_f° presents negative correlation, in agreement with Eqs. (13) and (16), index HBAS presents positive association, in agreement with Eqs. (15) and (16), and index *D'* presents negative correlation, in agreement with Eq. (16). The inclusion of index *S* positively correlates with the relative retention time and improves the fit [Eq. (18)], in agreement with Eq. (14). In Eq. (18), index ΔH_f° presents negative correlation, in agreement with Eqs. (13), (16) and (17), index HBAS shows a positive association, in agreement with Eqs. (15)–(17), index *D* presents negative correlation, in agreement with Eq. (17), and index *D'* shows a negative association, in agreement with Eqs. (16) and (17).

5. Conclusion

From the present results and discussion, the following conclusions can be drawn.

1. The objective of this study was to develop structure-property relationships for the qualitative and quantitative prediction of the reverse phase liquid chromatographic retention times of CGAs. It is hoped that the results of the present work increase scientific knowledge in the field of the relation prediction of chlorogenic acids in coffee. Program SCAP permits the Gibbs free energies of solvation (hydration) and partition coefficients that illustrate that for a certain atom, the solvation energies and partition coefficients result responsive to the occurrence in the molecule of some other atoms and groups.
2. The factors necessary to compute the co-ordination index result in the standard molar formation enthalpy, molecular mass and surface area.
3. Linear correlation models resulted for chromatographic retention times. The morphological and coordination indices provided strong multivariable linear regression equations for chromatographic retention. The trend between the coordination index and molecular weight points not only to a homogeneous molecular structure of chlorogenic acids but also to the ability to predict and tailor their properties. The latter is non-trivial in the analysis of chlorogenic acids and phenolic compounds in foods, beverages, human plasma, and urine because of the complex food, blood and urine matrixes.
4. The effect of different types of features was analyzed: thermodynamic, geometric, fractal, etc. The molar formation enthalpy, bare molecular and hydrophobic solvent-accessible surface areas, fractal dimensions, etc. distinguished chlorogenic acids in linear fits.

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