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In silico clastogenic activity of dietary phenolic acids

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ABSTRACT

Phenolic acids have been reported to exert multiple biological effects, including their activity as pro-oxidants. Structural alerts to identify the clastogenic activity of phenolic acids with pro-oxidant activity were determined in the current study. The described methodology was based on the application of a quantitative structure–activity relationship (QSAR) study. It was developed a virtual screening method based on a clastogenic model using the topological substructural molecular design (TOPS-MODE) approach. The model has presented a suitable probability of good classification for the external prediction data set. Therefore, it was possible to establish the structural criteria for maximal clastogenicity (chromosomal aberrations) of pro-oxidant reported phenolic acids. The two main criteria were represented by the presence of methoxy and/or hydroxyl substitutions on the benzene ring and polarity of these substituents. In summary, the apolar regions of phenolic acid derivatives contributed negatively to the activity, while the polar groups favored it.

1. Introduction

Most of the phenolic acids are dietary compounds with interesting benefits to health (Gaspar et al., 1996). Currently, these compounds have attracted considerable attention due to its broad biological and pharmacological activities, owing to their role as

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antioxidants and their implication in the prevention of pathologies such as cardiovascular diseases cancer and inflammatory disorders (Azam, Hadi, Khan, & Hadi, 2004). However, several published studies of exogenous antioxidants showed controversial results (Decker, 1997; Maurya & Devasagayam, 2010). In some cases beneficial attributes are overemphasized, being the exogenous polyphenolic antioxidants considered "double-edged swords" in cellular redox state (Bouayed & Bohn, 2010). The type, dosage and matrix of these compounds may be determinant factors in the balance between beneficial or deleterious effects (Bouayed & Bohn, 2010). It was also been reported that, under special conditions, an antioxidant could become a pro-oxidant that accelerate lipid peroxidation and/or induce DNA damage (Azmi, Bhat, & Hadi, 2005; Azam et al., 2004; Fukuhara & Miyata, 1998; Sakihama, Cohen, Grace, & Yamasaki, 2002; Yamashita, Tanemura, & Kawanishi, 1999). Phenolic acids are examples of substances with pro-oxidant report under certain conditions, such as high doses or presence of metal ions (Mozuraityte, Storrø, & Rustad, 2009; Sakihama et al., 2002; Simiæ, Manojloviæ, Šegan, & Todoroviæ, 2007). Because many of the results are inconclusive and sometimes contradictory, it has been suggested the need to clarify the safety aspects, structure-activity (Yordi, Molina, Matos, & Uriarte, 2012a, 2012b), bioavailability and metabolism of compounds with antioxidant activity when they become part of functional food or nutraceuticals. In this sense, and taking into account previous studies, it is interesting to predict, related to the structure-activity relationship, the DNA damage leading to pro-oxidant substances (Yordi et al., 2012a, 2012b). Aruoma (2003) described that oxidative modifications to DNA are an important biochemical process. It is known that one of the endpoints of the oxidation of this biomolecule is the chromosomal aberrations (Aruoma, 2003). These represent an early stage of carcinogenesis and may provide important oxidative stress (OS) biomarkers (Aruoma, 2003). Physical or chemical agents capable of inducing these mechanisms are called clastogens. The clastogen prediction (QSAR model), starting from a structural analysis, has been postulated by Estrada et al. (Estrada & Molina, 2006). Results of a virtual screening using QSAR methodology in which it was predicted the clastogenic activity and DNA damage of flavonoids with reported pro-oxidant activity had been published by (Yordi et al., 2012a, 2012b). Taking into account the different phenolic acids reported as pro-oxidants, the aim of this study was to identify structural alerts of clastogenic activity (chromosomal aberrations) using topological molecular descriptors and applying a previously described clastogenic model created and validated by Estrada and Molina (2006).

2. Materials and methods

2.1. Descriptors generation and feature selection

TOPS-MODE approach represents a useful platform for the automatic generation of structural alerts (Estrada & Molina, 2001). It is based on the calculation of spectral moments of molecular bond matrices appropriately weighted taking into account the hydrophobic, electronic and steric molecular features. Spectral moments are the trace of the kth power of a matrix, i.e., the sum of all the main diagonal entries of such matrices (Estrada & Molina, 2001). These matrices represent the molecular skeleton without taking into account hydrogen atoms. Bond weights are placed as diagonal entries of such matrices and represent quantitative contributions to different physic-chemical properties. Among bond weights currently in use in our approach, we have standard bond lengths (*SD*), standard bond dipole moments (*DM*), hydrophobicity (*H*), polar surface area (*PS*), polarizability (*Pol*), molar refractivity (*MR*), van der Waals radii (*vdW*), and Gasteiger–Marsilli charges (*Ch*). Descriptors were generated to each SMILE reported substances with pro-oxidant activity using MODESLAB software package version 2.0.

2.2. Classification model

A virtual screening was performed, in which a clastogenic structure-activity relationship model was used. The theoretic classification model that coded topological information in each spectral moment (μ) and bond weight (molecular descriptors) is represented by Eq. (1) and was prepared and validated by (Estrada & Molina, 2006). This model codifies topological information based on the TOPSMODE approach.

$$\begin{aligned} AC = {} & 0.0091\left[\Omega\left(\mu_1^{PS}\right)\right] - 1.5520\times10^{-4}\left[\Omega\left(\mu_5^{vdW}\right)\right] \\ & + 0.148\left[\Omega\left(\mu_4^{Ch}\right)\right] - 0.0021\left[\Omega\left(\mu_2^{PS}\right)\right] + 2.6261 \\ & \times10^{-4}\left[\Omega\left(\mu_3^{PS}\right)\right] - 3.8422\times10^{-5}\left[\Omega\left(\mu_4^{PS}\right)\right] + 1.1520 \\ & \times10^{-4}\left[\Omega\left(\mu_4^{MR}\right)\right] + 1.2011\times10^{-6}\left[\Omega\left(\mu_5^{PS}\right)\right] - 9.8202 \\ & \times10^{-5}\left[\Omega\left(\mu_5^{MR}\right)\right] - 3.8263\times10^{-5}\left[\Omega\left(\mu_8^{H}\right)\right] \\ & - 0.0626\left[\Omega\left(\mu_2^{Pol}\right)\right] + 1.6689\left[\Omega\left(\mu_1^{Pol}\right)\right] \\ & - 0.0078\left[\Omega\left(\mu_5^{Ch}\right)\right] + 0.1123\left[\Omega\left(\mu_3^{Ch}\right)\right] - 0.6517 \end{aligned} \quad (1)$$

AC indicates clastogenic activity. The Ω is used to indicate that the corresponding variable in brackets was orthogonalized respecting to the rest of the variables included in the model. μ_n are the spectral moments (molecular descriptors) and their exponents correspond to the bonds' properties mentioned before.

The classification model obtained is given below, together with the statistical parameters of the linear discriminate of the squared analysis, where λ is the Wilks' statistics, D^2 is the Mahalanobis distance and F is the Fisher ratio (Wilks'- $\lambda = 0.629$; $F(14.194) = 8.148$; $D^2 = 2.353$; $p < 0.0000$). The construction of this model by Estrada et al.(2006) was based in a data set of 372 organic compounds, including known carcinogens, presented in the groups of drugs, food, agrochemicals, additives, medicinal products,

Table 1
External data set (DS-1) of pro-oxidant phenolic acids reported.

No.	CAS numbers[a]	SMILE
1	614-60-8	OC(=O)C=CC1=CC=CC=C1O
2	501-98-4	C1=CC(=CC=C1C=CC(=O)O)O
3	14755-02-03	C(/C=C/C1=CC(=CC=C1)O) (=O)O
4	537-98-4	C(/C=C/C1=CC=C(O)C(=C1)OC) (=O)O
5	331-39-5	C(/C=C/C1=CC(=C(C=C1)O)O) (=O)O
6	69-72-7	OC(=O)C1=C(O)C=CC=C1
7	99-96-7	O=C(O)c1=CC=C(O)c=c1
8	306-08-1	C1(=C(C=CC(=C1)CC(=O)O)O)OC
9	530-57-4	C1(=C(C=C(C=C1OC)C(=O)O)OC)O
10	99-50-3	C(C1=CC=C(O)C(=C1)O) (=O)O
11	149-91-7	C1(=C(C=C(C(=O)O)C=C1O)O)O
12	327-97-9	(CC(OC(/C=C/C1=CC(=C(C=C1)O)O)=O)C(C(C2)O)O) (C(=O)O)O
13	99-06-09	OC(=O)C1=CC(=CC=C1)O
14	476-66-4	C13=C4OC(=O)C2=CC(=C(C(=C12)OC(C3=CC(=C4O)O)=O)O)O
15	530-59-6	COC1=CC(/C=C/C(O)=O=CC(OC)=C1O

[a] CAS, chemical abstracts service.