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ORIGINAL ARTICLE

A theoretical assessment of antioxidant capacity of flavonoids by means of local hyper–softness

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Abstract A theoretical reactivity descriptor to estimate local reactivity on molecules was tested to assess the antioxidant capability of some flavonoids. It was validated by comparison with experimental precedents published already by Firuzi et al. (2005). The aforementioned reactivity index is called local hyper-softness (LHS). This parameter was applied on HO- substituent groups on the same set of flavonoids within each subclassification: flavones (apigenin and baicalein), flavonols (fisetin, galangin, 3–OH flavone, kaempferol, myricetin, and quercetin), flavanones (hesperetin, naringenin, taxifolin) and isoflavones (daidzein and genistein). Experimental values of both techniques, ferric reducing antioxidant power (FRAP) and anodic oxidation potential (E_{ap}) were retrieved from Firuzi et al. (2005) with the purpose of validating the calculated LHS values. Excepting myricetin, the LHS values of all these compounds matched in a similar order relationship experimentally obtained by means of E_{ap} and FRAP from Firuzi et al. (2005). Our results revealed that LHS is a suitable theoretical parameter to get an insight concerning to the antioxidant capacity of these compounds, in particular, LHS allows explaining experimentally obtained values of FRAP along with E_{ap} values in terms of reactivity of HO- substituent groups belonging these molecules theoretically computed without including experimental parametes.

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1. Introduction

1.1. Relevance of flavonoids

Flavonoids are polyphenols of varied structure that can be found as aglycones or glycosides. They are secondary metabolites present in many fruits and vegetables. In plants, they play different functions as protection of UV light, defense of abiotic

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tensions, bacterial phytopathogens, and fungi; the most recently properties found revealed they can act as the endogenous regulator of the movement of auxins in plants (Brunetti et al., 2013; Jansen et al., 1998). Flavonoids have been studied due to their many pharmacological activities such as antioxidants, antibacterial, antimutagenic, antiangiogenic, anti–inflammatory, antiallergic, modulators of enzymatic activity and anticancer activity (Cushnie and Lamb, 2011; Ribeiro et al., 2013; Kawai et al., 2007). Several studies have shown that flavonoids can interact with different therapeutic targets, this ability to interact is principally influenced by their chemical structure and REDOX capacity (García-Lafuente et al., 2009). Some examples of enzymes that may be inhibited are NADH oxidases, polyphenol oxidases, peroxidases, lipoxygenase, cellulases, xylanases, pectinases, glutathione-S-transferases, glycoproteins, and kinases (Ravishankar et al., 2013). Considering the importance flavonoids is that in our group has been interested in last years in the study of interaction and inhibition of important enzymes involved in the arachidonic acid cascade as are the lipoxygenases (LOX).

Therefore, flavonoids appear as attractive molecules because they possess many of the desired structural characteristics aforementioned, for instance: genistein, luteolin, apigenin or kaempferol (Peterson and Dwyer, 1998) and all of them have an important antioxidant capacity. On the other hand, we can mention that biological studies of flavones and isoflavones carried out by our group showed that exist a direct relationship between the structure of inhibitors and LOX inhibition (Mascayano et al., 2011; Mascayano et al., 2015; Ribeiro et al., 2014). Also, results of antioxidant of some natural flavonoids were previously published by Firuzi et al. (2005) and taken into account in this work with the aim to obtain relevant electronic information by quantum chemistry, which could provide an explanation of the structure–activity relationship between flavonoids. According to the latter, our purpose is to reveal locally and theoretically the reactivity on different sites on a molecule. Although a typical local reactivity index corresponds to the net charges coming from a population analysis, as the latter has demonstrated to be not too well connected with an experimental parameter (Martínez-Araya et al., 2015), through the Conceptual DFT (Parr and Yang, 1989; Geerlings et al., 2003), a local reactivity descriptor to assess the antioxidant capability of some flavonoids was proposed by Morell et al. (2005) to get insights concerning to the antioxidant capacity and that local reactivity descriptor is known as the local hyper–softness (LHS) and its definition will be given in the next subsection.

1.2. Local hyper–softness

There are many indexes to estimate reactivity theoretically from quantum chemical calculations coming from the field of the Density Functional Theory (Hohenberg and Kohn, 1964; Kohn and Sham, 1965) (DFT) and as a consequence chemists can find a plethora of reactivity descriptors (Chermette, 1999) so giving rise to the Conceptual DFT (Parr and Yang, 1989; Geerlings et al., 2003) under the hypothesis that the total energy E of a system depends upon the total number of electrons N and the external potential $\upsilon(\mathbf{r})$, so that the application of successive ordinary and functional derivatives yields a wide range of reactivity descriptors which are divided into three types: global, local and non–local, all of them based on two essential physical observable quantities: energy, electronic density or both.

Among of the endless type of local reactivity descriptors that are possible to conceive, there is one defined at a third order (Geerlings and De Proft, 2008) that has had becoming more and more popular among some researchers interested in measuring local reactivities; this alluded descriptor is the so–called dual descriptor (Morell et al., 2005; Fuentealba and Parr, 1991; Morell et al., 2006) which has demonstrated to be a more robust tool than Fukui functions (Morell et al., 2008; Morell et al., 2008; Martínez-Araya, 2015). But certain limitations (Cárdenas et al., 2009) prevent its use to compare reactivity among different molecular systems. In fact, it can only be used to reveal nucleophilic and electrophilic sites on a molecule in order to understand its intrinsic reactivity without expecting to compare that reactivity with the local reactivity of another molecular system even using exactly the same reactivity descriptor. However, dual descriptor allows to define a more useful descriptor, so that in order to overcome the aforementioned limitation of dual descriptor, such an descriptor contains the dual descriptor in its definition along with a global reactivity descriptor giving rise to the local hyper–softness (LHS), this being the local reactivity descriptor that has assumed the role of dual descriptor when a comparison of local reactivities among different molecules is carried out (Martínez-Araya et al., 2015; Cárdenas et al., 2009; Martínez-Araya, 2013). LHS is represented by $s^{(2)}(\mathbf{r})$ and it is defined by the following operational formula:

$$s^{(2)}(\mathbf{r}) \approx f^{(2)}(\mathbf{r})\, S^2 = \frac{\rho(\mathbf{r})_{\mathrm{LUMO}} - \rho(\mathbf{r})_{\mathrm{HOMO}}}{\left(\varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}}\right)^2}. \quad (1)$$

The use of Eq. (1) implies to assume that global and local reactivity of a molecule is driven by frontier molecular orbitals (details about deduction of this operational formula are described in Supplementary Material). This is a good first approach to get an insight into a family of molecules.

Previous studies focused on the local reactivity of flavonoids through the use of the Conceptual DFT revealed information concerning to susceptible sites on a molecule to undergo nucleophilic and electrophilic attacks, in particular one flavonoid like naringenin was the main subject of analysis (Martínez-Araya et al., 2013; Glossman-Mitnik, 2013) and isonaringin (Glossman-Mitnik, 2014), however these works did not broach a family of flavonoids. Even so, that led us to take LHS into account whose operational formula given by Eq. (1) includes energies and electronic densities of frontier molecular orbitals under the hypothesis that reactivity is ruled by these molecular orbitals mainly and as a consequence the electron donor and electron acceptor capabilities of molecules can be computed through that descriptor, so that the antioxidant capacity can be attributable to the electron donor capacity of the molecule under study. Some molecules of biological interest like oxicams have been studied by means of the LHS descriptor (Martínez-Araya et al., 2013), thus revealing the most susceptible sites of these molecules to undergo nucleophilic and electrophilic attacks. Nevertheless there was no an intention to find a possible link with an experimental parameter. According to this precedent, our work points towards to explore a possible link between experimental parameters designed to measure antioxidant capacity of

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