



Antioxidant properties comparative study of natural hydroxycinnamic acids and structurally modified derivatives: Computational insights



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ABSTRACT

Density functional theory (DFT) and time-dependent formulation of DFT (TDDFT) have been used to explore the antioxidant and absorption properties, respectively of naturally occurring cinnamic acids, caffeic and ferulic acids, and some derivatives recently synthesized from a structural modification of the ethylenic spacer between the aromatic ring and the carboxylic functionality. The main mechanisms proposed in the literature for the antioxidant action of polyphenols as radical scavengers, that are hydrogen atom transfer (HAT), electron transfer followed by proton transfer (SET-PT), and sequential proton loss electron transfer (SPLET), were discussed in details. From the outcomes the HAT mechanism results to be the most probable one for the antioxidant action of this class of compounds. The simulated UV–Vis spectra are characterized by a broad band centered around 340 and 380 nm for naturally occurring and synthesized compounds, respectively, generated by a H → L electronic transition. The absorption spectra of natural antioxidants are in good agreement with the experimental counterpart, supporting the reliability of the spectra computed at TDDFT level of theory also for the derivatives. One of the derivative has been identified as the most promising candidate as antioxidant. Accordingly, our calculations encourage the synthesis of derivatives arising from *ad-hoc* structural modifications which could improve the antioxidant properties.

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1. Introduction

In the last twenty years there has been a growing attention on the role of free radicals in biology, as they are able to damage the most important macromolecules of the human organism. They are mainly produced from normal essential metabolic processes in the aerobic living organisms, usually as reactive oxygen species (ROS), reactive nitrogen species (RNS) and reactive sulfur species (RSS). Hence they are naturally present in the human organism, and exert a beneficial effect at low/moderate concentrations in defense against infectious agents and in the function of a number of cellular signaling systems. ROS can be produced also by extracellular stress, such as irradiation, air pollutants, and exposure to toxic agents [1,2]. In a normal, healthy organism or human body, the generation of prooxidants in the form of ROS and RNS are effectively kept in check by the various levels of antioxidant defense, which guarantee a balance between produced and neutralized highly reactive species. However, when this ratio is threatened such reactive species can attack proteins, lipids, DNA, RNA and sug-

ars causing the so called oxidative stress of body cells [2,3], which is implicated in a several human diseases [2,4,5].

In recent years, the possible role of nutrition in prevention of human diseases has taken a leading role. An external supplement of antioxidants has been indicated as a suitable way to maintain the concentration of free radicals as low as possible and then avoiding the oxidative stress [6]. Indeed, in the last years several studies have reported the beneficial effects of antioxidants on human health, including anticancer, anti-inflammatory, antibacterial, antiviral, cardioprotective and neuroprotective properties [7–12], just associated with their ability of preventing oxidative stress (OS). There is also evidence supporting their potential therapeutic use on diseases, such as diabetes, osteoporosis, arthritis, and cataract [13–16]. Their action is exerted by reacting with highly reactive species forming more stable and innocuous radicals for cells with respect to the inhibited ones, or turning off the radical chain reactions, helping to prevent the attack of such a species to biological macromolecules, limiting their damages.

It is widely established that the most essential structural characteristics which provide effective antioxidant activity are the presence of phenolic OH groups, which enhance the ability of such a molecules to quench the free radicals. Plants produce thousands

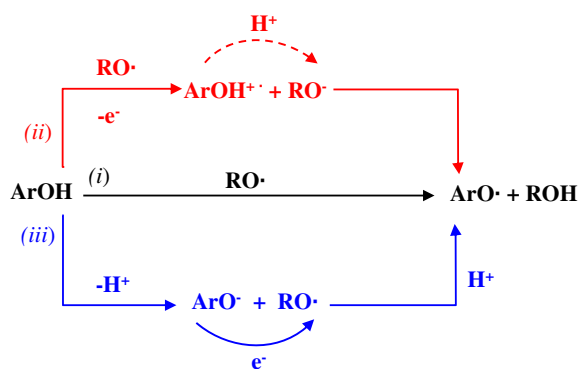
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of phenolic compounds as secondary metabolites [17] and consequently they are naturally present in fruits, vegetables and cereals. Hence, there are several naturally occurring compounds that present the structural characteristics needed to exert the role of free radical scavenger. Among them phenolic acids, benzoic and cinnamic acid derivatives, have been found to have very good antioxidant properties [18,19].

Phenolic compounds (ArOH) can exert the free radical scavenging activity by following essentially three important mechanisms (see Scheme 1): (i) the hydrogen atom transfer (HAT) in which the radical abstract the hydrogen from the antioxidant molecule in one single step; (ii) the single-electron transfer followed by proton transfer (SET-PT), which takes place in two steps: first the radical cation $\text{ArOH}^{+\bullet}$ is formed via electron transfer from the antioxidant to the free radical, and then it deprotonates yielding the ArO^\bullet radical, followed by ROH formation; (iii) the sequential proton loss electron transfer (SPLET) takes place through two consecutive steps that are deprotonation of the phenolic compound and the consecutive electron transfer from the phenoxide anion to RO^\bullet to form the phenoxy radical. On the basis of theoretical calculations, the HAT mechanism has been proposed as a key reaction mechanism in the antioxidant activity of several compounds, not only polyphenols [20] and derivatives [21–27], but also non-phenolic compounds [28–30]. Anyhow, it is noteworthy that the other reaction mechanisms yield to the same products as HAT, and properly discriminating among them could be a complex task.

Other important information on the working mechanism of antioxidants can come from the knowledge of the frontier orbital energies, E_{HOMO} and E_{LUMO} , and distributions. The lower HOMO energy is responsible for the minor ability of a molecule to donate a proton. On the contrary, an higher HOMO energy implies that the molecule is a good electron donor. Since the H-abstraction reaction



Scheme 1. Schematic representation of (i) HAT, (ii) SET-PT and (iii) SPLET mechanisms.

involves the electron transfer, the HOMO composition of a phenolic compound can give a qualitative idea of which sites are easily attacked by free radicals and other reactive agents. From the difference between HOMO and LUMO energies, indication about chemical activity of the molecule can be extracted. The lower $\Delta E_{\text{H-L}}$ is connected with lower antioxidant activity of the molecule [31].

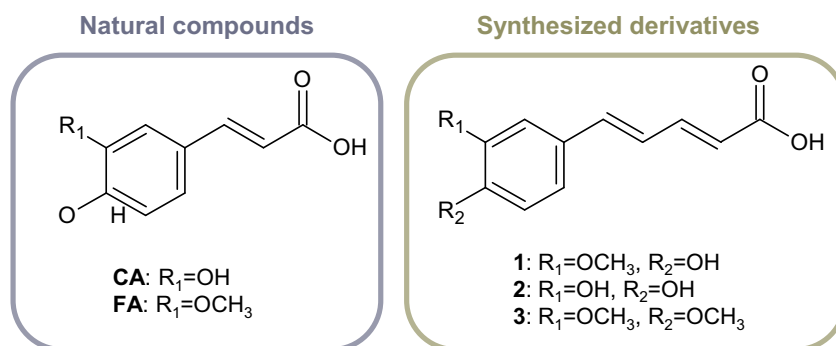
In spite of the enormous number of compounds known to exert antioxidant properties, the synthesis of molecules that combine structural characteristics, and then beneficial effects, introducing modifications to naturally occurring antioxidants is becoming an increasingly robust strategy to achieve compounds with enhanced biological activities, as well as therapeutic potential [32–36].

Chavarria et al. [36] have exploited the significantly high antioxidative efficiency of the hydroxycinnamic acids [37], characterized by the presence of the $\text{CH}=\text{CH}-\text{COOH}$ group, to synthesize derivatives compounds with improved antioxidant activity. Therefore, aiming at enhancing the absorption, distribution, metabolism and excretion (ADME), they have modeled the cinnamic acid scaffold in such a way to extend the ethylenic spacer between the aromatic ring and the carboxylic acid functionality (see Scheme 2). In this work, they have evaluated several properties, such as radical scavenging activity, redox properties, iron(II) chelating activity, octanol/water partition coefficient, cytotoxicity and neuroprotection in a cellular model, of caffeic (CA) and ferulic acids (FA) and their synthesized derivatives (1–3). The obtained results highlight the potential of the derivatives as drugs for the treatment of oxidative stress associated diseases, especially as neuroprotective agents.

As the theoretical evaluation of intrinsic properties of such a compounds can help to gain more insight on their preferred action mechanism, we report here a systematic DFT-based study on such a compounds. In our investigation, the relationship between the experimental radical scavenging activity of cinnamic and ferulic acids, CA and FA, and derivatives 1–3 has been interpreted in terms of some key thermochemical parameters (BDE, IP, PDE, PA and ETE). The comparison between the scavenging activity of the natural antioxidants and their recently synthesized derivatives [36] have been also reported. In addition, the simulation of UV–Vis absorption spectra has been provided in order to help their identification.

2. Computational details

All the electronic calculations have been performed using the Gaussian 09 computational package [38]. The geometries of all the investigated compounds, including radicals, radical cations, and anions, have been fully optimized employing the hybrid functional M05-2X [39] combined with the standard 6-31+G** basis set. Such a functional has been also suggested, together with other



Scheme 2.

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