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Exploiting the cyclodextrins ability for antioxidants encapsulation: A computational approach to carnosol and carnosic acid embedding

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ABSTRACT

Cyclodextrins (CD) are widely used as encapsulation agents for bioactive molecules. Here, we use docking and quantum chemical calculations to ascertain the capability of the three available CDs (α-, β- and γ-CD) to encapsulate carnosol and carnosic acid, which are the most important antioxidants present in the rosemary extract. Docking is revealed as an efficient tool to rank best suited candidates as it quickly discards the molecules that do not fit into CDs cavity. However, more accurate quantum calculations are required to refine the molecular structure as well as to provide reliable interaction energies. According to the reported data, further investigations into the encapsulation of the rosemary extract should be focused on β- and γ-CD rather than in the smaller α-CD, specially if one looks to efficiently preserve their high antioxidant activity.

1. Introduction

Plants offer a vast source of natural compounds, many of them with potential medical applications [1,2]. One excellent example is the rosemary extract, which has been shown to exert several beneficial effects, including the inhibition of cancer cells proliferation [3,4], antimicrobial, antiviral and antiinflamatory properties [5–7], obesity prevention [8,9] and antioxidant activity, that is, to its free radical ($R^{\cdot}$) scavenging action [10]. Indeed, the bioactivity of rosemary extract has been attributed to its antioxidant properties [11,12]. Rosemary extract analyses have led to the identification of over seventeen compounds which belong to three main classes of constituents: phenolic diterpenes, flavonoids and diterpenes [13]. Among them, two diterpenes derivatives, carnosic acid and carnosol (see Fig. 1), have been reported to be important anticancer agents [14–17] while simultaneously being responsible for about 90% of the whole antioxidant activity of rosemary [18].

Most free radicals $R^{\cdot}$ in living systems are derived from reactive oxygen and reactive nitrogen species [19,20]. In that framework, antioxidants balance the production of radicals to keep them at the optimal biological concentration [21]. There are three mechanisms to neutralize $R^{\cdot}$ [22]: single electron transfer [Eq. (1)], hydrogen atom transfer [Eq. (2)] and radical addition to a double bond [Eq. (3)]:

$$ATX + R^{\cdot} \rightarrow ATX^{\cdot+} + R^{-} \quad (1)$$

$$ATX + R^{\cdot} \rightarrow ATX^{\cdot}(-H) + RH \quad (2)$$

$$ATX + R^{\cdot} \rightarrow [ATX - R]^{\cdot} \quad (3)$$

where *ATX* stands for a standard antioxidant. The predominant mechanism depends on many factors, e.g., the chemical nature of the antioxidant and the free radical, the media polarity, the pH, etc. [23,24].

An efficient antioxidant is characterized by a high reactivity, ubiquity, versatility, ability to cross physiologic barriers and biological availability [21]. However, antioxidants must reach the action site (i.e., a damaged tissue with an excess of $R^{\cdot}$) without structural degradation if an efficient biological activity is looked for. An emerging idea is to protect the antioxidant molecule from side reactions by using an encapsulation agent [25]. Among all encapsulation materials, cyclodextrins (CDs) are one of the best suited molecules for embedding antioxidants since they not only protect them from early deactivation processes but also improve their aqueous solubility [26–29]. CDs are cyclic oligosaccharides, composed by glucopyranose subunits linked by α-(1,4) bonds. There are three commercially available CDs: α-CD, β-CD and

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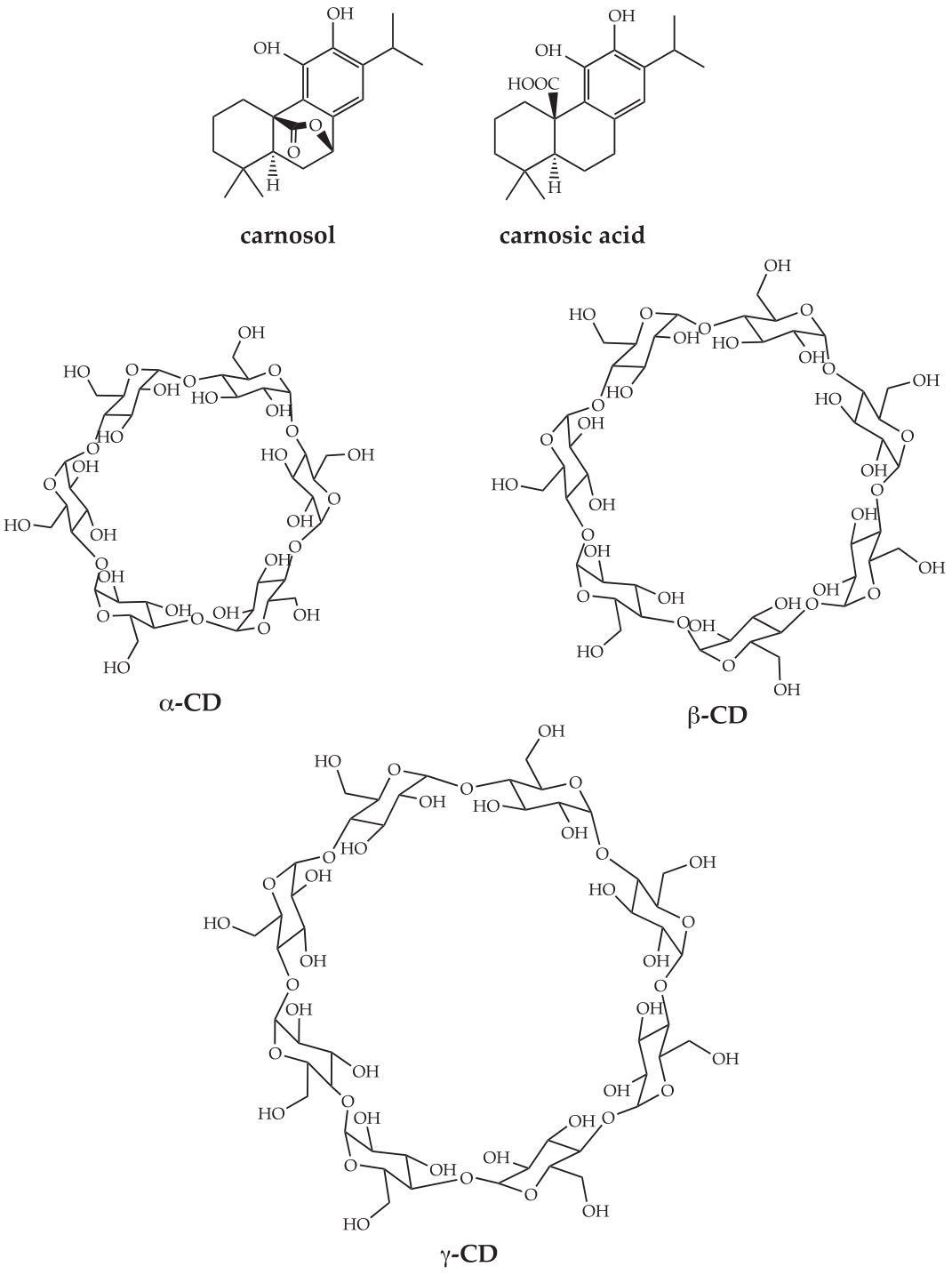

Fig. 1. Chemical structures of the two main active antioxidants present in rosemary acid (carnosol and carnosic acid) and the three available cyclodextrins (α-, β- and γ-CD).

γ-CD, composed of six, seven and eight glycosyl units respectively. As schematized in Fig. 1, CDs adopt a round structure with an external hydrophilic surface and one lipophilic cavity core [30]. As recently reviewed by Pinho and co-workers, the CDs encapsulation ability is governed by the hydrophobic cavity in which many molecules with biological activity might be embedded, including essential oils, alkaloids, phenolic acid derivatives and flavonoids [31]. In the same vein, Ionita et al. [32] have experimentally measured the antioxidant activity of rosemary extracts entrapped in polymeric systems of polyethylene glycol and β-CD. According to their results, CDs might be also used as encapsulation agents for diterpenes. However, until now there is no information about the molecular mechanism behind the encapsulation of carnosol and carnosic acid into CDs.

In the present work, molecular simulations have been performed to assess the capabilities of CDs to encapsulate carnosol and carnosic acid antioxidants. More specifically, we have used docking, quantum mechanical (QM) and hybrid QM:QM' calculations to determine the structure of the antioxidant-CD complexes and their interaction energies. The present computational study is completed with a non-covalent interaction (NCI) analysis to disclose the chemical contacts that govern the encapsulation ability of CDs.

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