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Modelling of tyrosol and hydroxytyrosol based lipopolyphenols as new guest molecules for cyclodextrin nanoencapsulation

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INTRODUCTION

Tyrosol (Ty) and **hydroxytyrosol** (HTy) are natural antioxidants found in various sources such as olive oils and grapes/wines. In olives, HTy is bound in a glycosyl-*seco*-iridoid derivative, named oleuropein, the main bitter compound in olives. Ty and HTy have relatively low hydrophobicity (log*P* of 1.48 and 1.19, respectively) and the increase of their bioavailability and compatibility with hydrophobic formulations (food, pharmaceutical or cosmetic formulations) can be achieved by derivatization to their corresponding fatty acid (FA) esters (***lipopolyphenol bioconjugates***). Moreover, the controlled release of these antioxidant compounds in various matrices can be performed by **cyclodextrin** (CD) **nanoencapsulation**.

Goal: In the present study three series of Ty, HTy and MeHTy esters with short-, medium- and long-chain FAs were selected for the evaluation of the influence of the structural characteristics to the antioxidant activity, as well as their capability to molecular encapsulate in natural α- and β-CD.

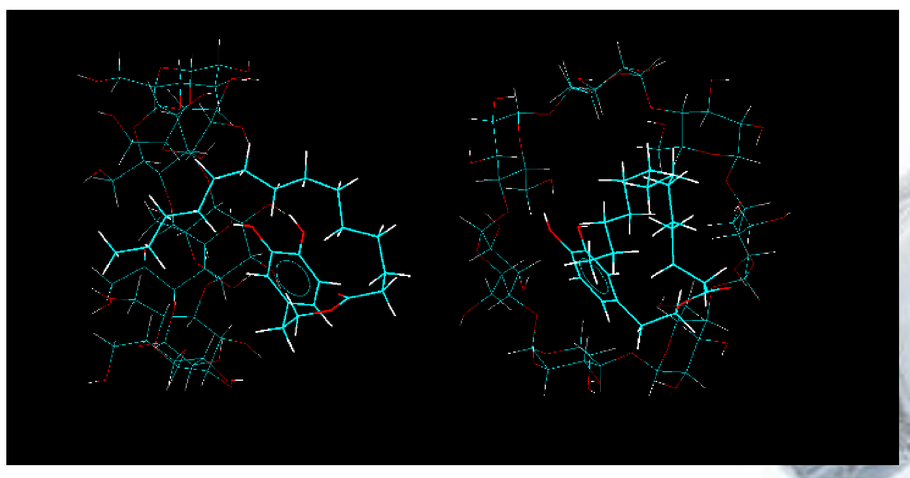

Figure 1. Optimized β-CD/HTyC14 lipopoliphenol derivative complex, obtained by *MM+* molecular docking (views along *OX* and *OZ* axes; HTyC14 lipopolyphenol bioconjugate is in bold)

RESULTS AND DISCUSSION

Molecular modeling of lipopolypehnols revealed a *self-hydrophobic interaction* for medium- and long-chain FA derivatives between the FA and phenyl moieties. The best interactions with α- and β-CD were obtained for C_{14} lipopolyphenol derivatives (Figure 1), with interaction energies of 20.3 and 24.2 kcal/mol for α- and β-CD complexes with ***hydroxytyrosol-myristic acid bioconjugate*** (HTyC14) and 24.9 kcal/mol for β-CD/HTyC14. On the other hand, *charged surface area* [4] or *autocorrelational descriptors* of the studied lipopolyphenols have significant influences to the antioxidant activity (Eq. 1 for HTy lipopolyphenol derivative series, r = 0.78 for the *RNCS* descriptor - relative negative charge surface area, and Eq. 2 for HTy and MeHTy lipopolyphenol derivative series, r = 0.83 for the *ATSC8c* descriptor - centered Broto-Moreau autocorrelation 8, weighted by charges).

MATERIALS AND METHOD

Lipopolyphenol bioconjugates presented antioxidant activity expressed as radical scavenging capacity (*RSC*), compared to trolox (μM trolox/mM) or as 50% *RSC* (μM), which was converted to p(RSC_{50}) [1-3]. C_2 to C_{18} saturated FA esters of Ty, HTy and MeHTy were considered.

All compounds were molecular modelled by *MM+ Molecular Mechanics* module in HyperChem 7.52, while the most stable conformers were obtained by *Conformational Analysis* module in the same package. The structural descriptors were determined by *QSAR Properties* in HyperChem and *PaDEL Descriptors*.

RSC parameters were correlated with these structural descriptors and the best **QSAR models** were retained.

On the other hand, relevant molecules were subjected to molecular docking in α- and β-CD, using a CD:lipopolyphenol bioconjugate molecular ratio of 1:1 (to the CD secondary face, along *OZ* axis, with distance between the gravity centers of molecules of ~8 Å).

$$RSC\ (\mu\text{M trolox/mM})_i = -148.8 + 97.96(\pm 29.30) \cdot RNCS_i \quad \text{[Eq. 1]}$$

n = 9, r = 0.784, F = 11.2, p < 0.02, s = 196.4

$$p(RSC_{50})_i = 4.69(\pm 0.04) + 2.27(\pm 0.45) \cdot ATSC8c_i \quad \text{[Eq. 2]}$$

n = 13, r = 0.833, F = 24.9, p < 0.0005, s = 0.08

CONCLUSION

These findings suggests using **CDs** as *protecting* and *controlled release* **natural matrices** for applying **lipopolyphenol bioconjugates** with enhanced bioavailability to ***innovative food*** and ***pharmaceutical formulations***.

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