COMPARATIVE NMR STUDY OF THE COMPLEXATION OF QUERCETIN WITH TWO B-CD

Konstantina Manta [†,]; Paraskevi Papakyriakopoulou [†,]; Maria Chountoulesi [†]; Dimitrios A. Diamantis [‡]; Dimitrios Spaneas[†], Vasiliki Vakali [‖]; Nikolaos Naziris [†]; Maria V. Chatziathanasiadou [‡]; Ioannis Andreadelis[‖], Kalliopi Moschovou[‖], Ioanna Athanasiadou [†]; Paraskevas Dallas [†]; Dimitrios M. Rekkas [†]; Costas Demetzos [†]; Gaia Colombo[*]; Uros Javornik [§], Janez Plavec [§]; Thomas Mavromoustakos [‖]; Andreas G. Tzakos [‡]; Georgia Valsami[†]

† Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, Zografou 15771, Greece
‖ Department of Chemistry, School of Sciences, National and Kapodistrian University of Athens, Panepistimiopolis Zografou 15771, Greece
‡ Department of Chemistry, Section of Organic Chemistry and Biochemistry, University of Ioannina, Ioannina 45110, Greece
* Department of Life Sciences and Biotechnology, University of Ferrara, Italy,
§ Slovenian NMR Centre, National Institute of Chemistry, Slovenia

Abstract: Quercetin, is a flavonoid associated with high oxygen radical scavenging activity, and potential neuroprotective agent against Alzheimer's disease. Quercetin's low water-solubility and bioavailability, and extended peripheral metabolism make nasal administration promising to overcome blood-brain barrier, achieving therapeutic brain concentrations. The formation of Quercetin-Hydroxypropyl-β-Cyclodextrin (Que-HP-β-CD) complexes, increases molecule's solubility and stability, and probably also its mucosal permeability. Quercetin-Methyl-β-Cyclodextrin (Que-Me-β-CD) inclusion complexes were prepared, characterized and compared with the Que-HP-β-CD complex, using biophysical and computational methods, as candidates for preparation of nose-to-brain Quercetin's delivery systems. DSC thermograms, NMR and fluorescence Spectroscopy, MDS confirmed inclusion complex formation of Quercetin with both CDs. Differences between the two preparations were observed regarding their thermodynamic stability, and inclusion mode governing the details of molecular interactions. Quercetin's solubility at pH 1.2 and 4.5 was similar and linearly increased with both CD concentration. At pH 6.8 Que's solubility was higher and positively deviating from linearity in presence of HP-β-CD than in Me-β-CD, possibly revealing the presence of more HP-β-CD molecules in complex formation. Overall, water-solubility of lyophilized Que-Me-β-CD and Que-HP-β-CD products was approximately 7-40 times and 14-50 times higher than pure Quercetin at pH 1.2-6.8. In addition, the *ex-vivo* permeation from rabbit nasal mucosa proof of concept experiment revealed measurable and similar Que permeability profile with both CDs and negligible permeation of pure Que.