Integrating “spicy” cyclodextrin inclusion complexes into the treatment of cancer: X-ray crystallographic analysis of Piperine and Capsaicin in native and methylated beta-cyclodextrins

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Introduction: Piperine (PN) and Capsaicin (CP) are natural products endowed with antimicrobial, antiviral, anti-inflammatory, but most importantly, anticancer activity [1]. Cyclodextrins (CDs) are used in pharmaceutical industry to incorporate apolar molecules inside their hydrophobic cavity, increasing the aqueous solubility of the encapsulated guests and thus enhancing their bioavailability and therapeutic potential [2]. Our recent findings, that indicate more pronounced anticancer activity for PN and CP in their complexed form with parental β-CD and its methylated derivative (DM-β-CD) against two cell lines, impelled us to study their structure in an effort to map the structure-function relationships.

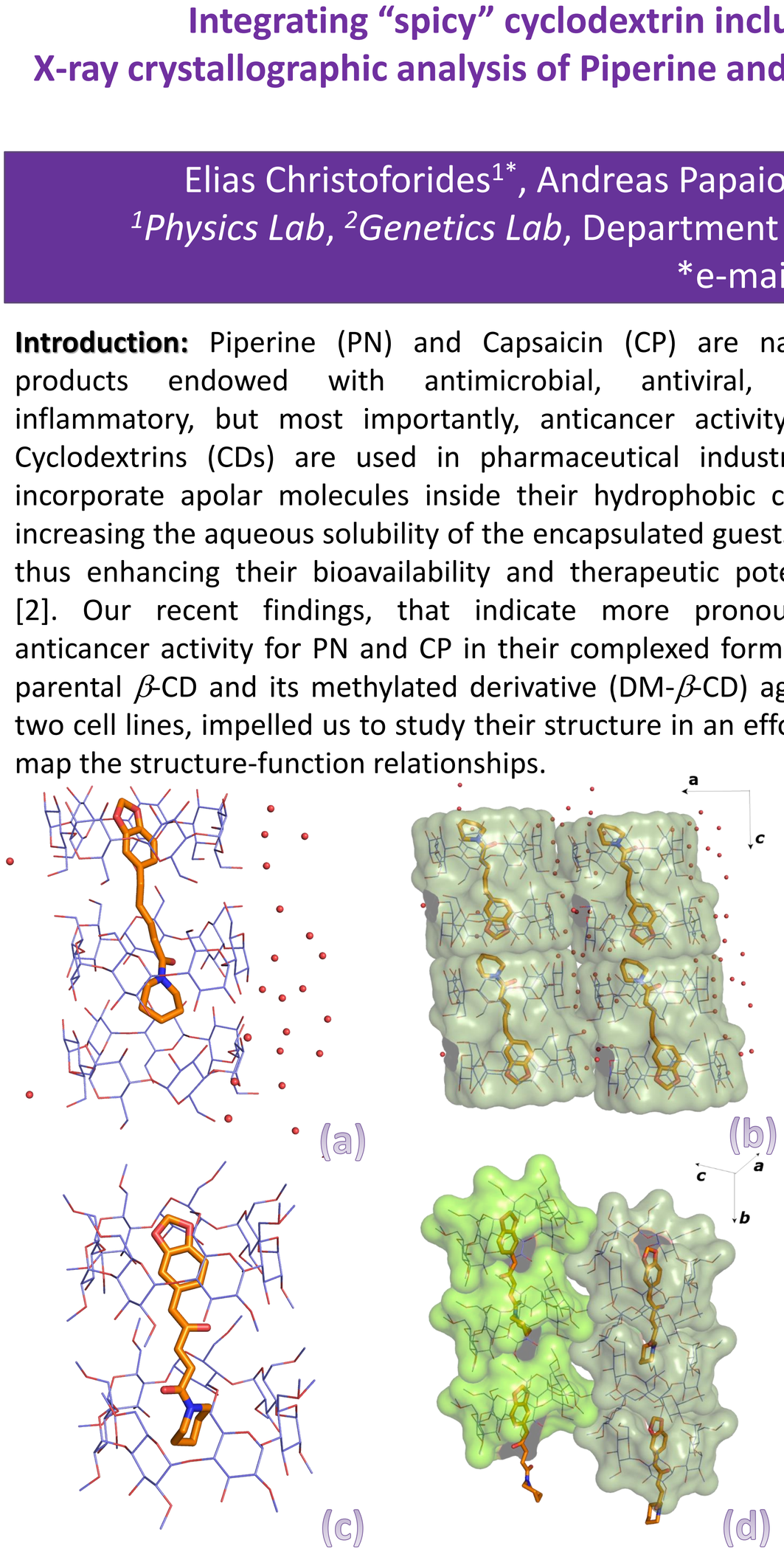

Figure 1

X-ray crystallographic analysis of Piperine/CD complexes: In the PN/β-CD inclusion complex, two adjacent hosts form a head-to-head dimer along the *a* axis and the guest is found ‘axially’ accommodated inside two dimeric cavities (**Fig. 1a**). The 22 waters stabilize the complex units which are arranged in a Channel (*CH*) packing mode (**Fig. 1b**). In the PN/DM-β-CD case, PN is hosted inside two successive DM-β-CDs arranged in a head-to-tail mode along the 2-fold screw *a*-axis, with its 1,3-Benzodioxole moiety entering the cavity of the “upper” DM-β-CD and the piperidine ring penetrating the “below” host’s cavity **(Fig. 1c and d**).

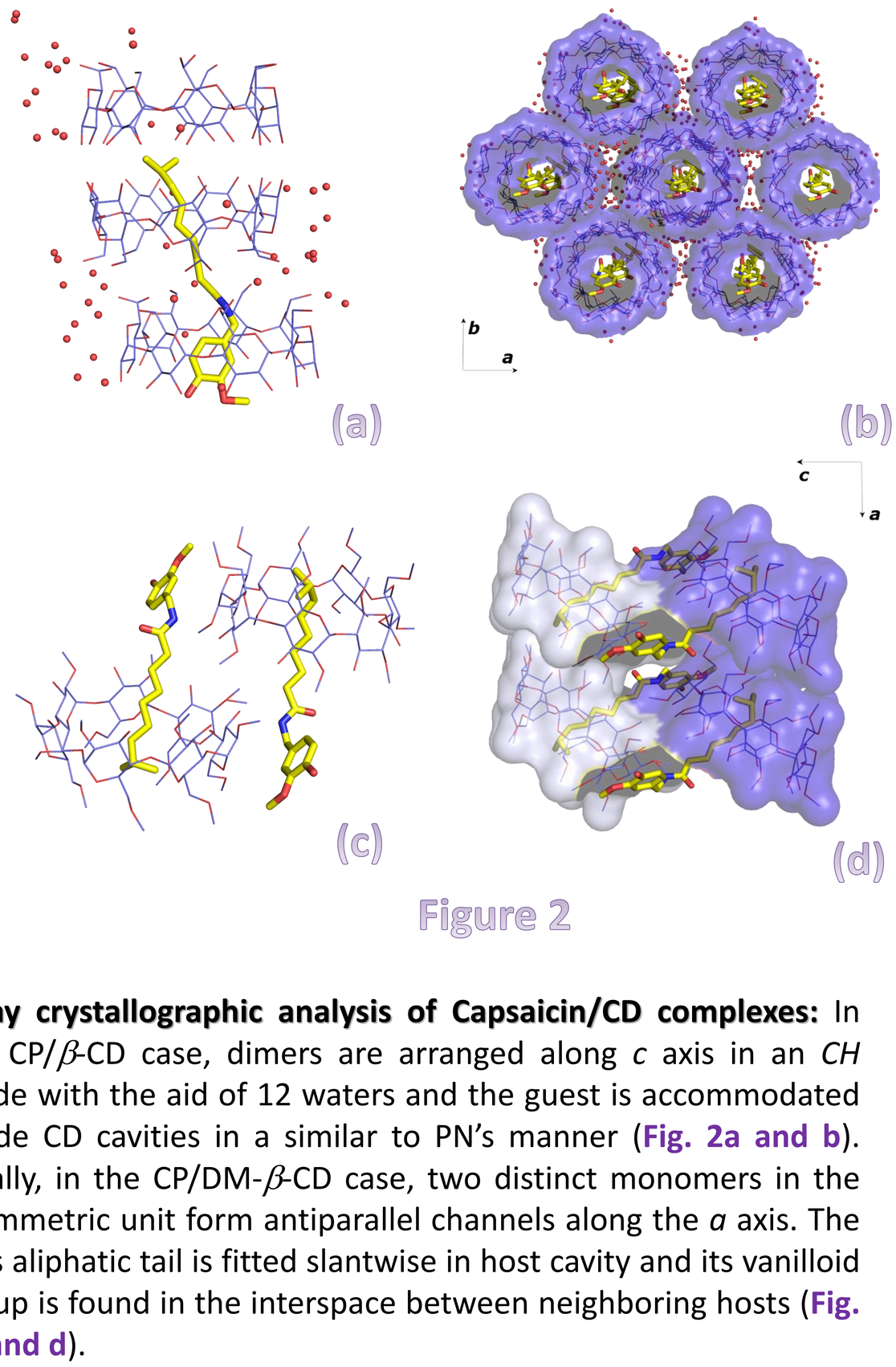

Figure 2

X-ray crystallographic analysis of Capsaicin/CD complexes: In the CP/β-CD case, dimers are arranged along *c* axis in an *CH* mode with the aid of 12 waters and the guest is accommodated inside CD cavities in a similar to PN’s manner (**Fig. 2a and b**). Finally, in the CP/DM-β-CD case, two distinct monomers in the asymmetric unit form antiparallel channels along the *a* axis. The CP’s aliphatic tail is fitted slantwise in host cavity and its vanilloid group is found in the interspace between neighboring hosts (**Fig. 2c and d**).

Conclusions: The 3D structures of the inclusion complexes of both Piperine and Capsaicin molecules in native and modified β-CDs are presented here. The availability of the structural details of the binding of these natural products in cyclodextrins, may be useful in understanding the improved bioavailability and therapeutic index of such complexes against certain cancer cell lines.

References:

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