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Molecular docking predicting the C-phycocyanin role on pro-apoptotic proteins

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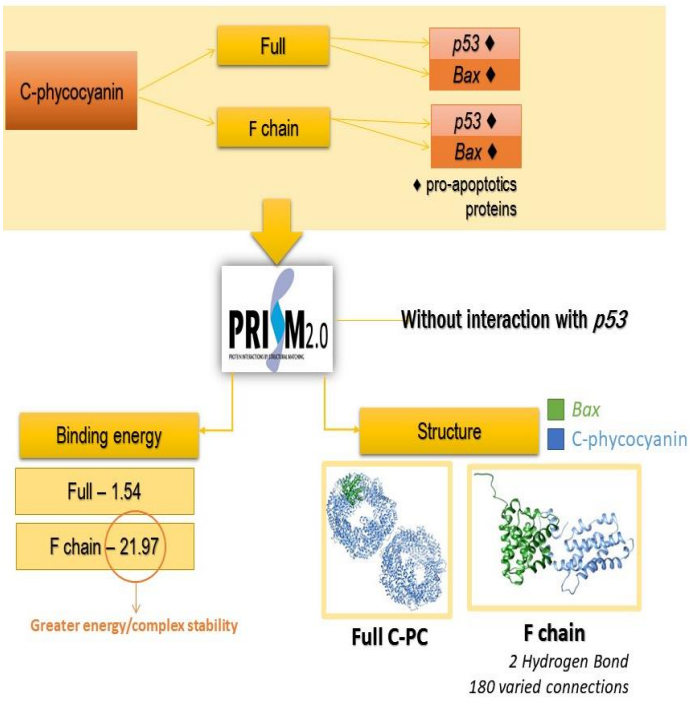
Graphical Abstract



Abstract. *Bax and p53 proteins are interesting therapeutic targets, as they signal apoptosis and prevent neoplasms. In most cancers, these proteins are downregulated to support tumor survival. A C-phycpcyanin (C-PC) is a phycobiliprotein with diverse biological activities and could upregulate Bax and P53 in tumor cells. To assess the interaction between C-PC and pro-apoptotic proteins, docking is a valuable screening tool avoiding time and resources spent on in vitro experiments if this interaction does not occur in silico. Using PRISM web server (algorithm based on structural matching) the interaction of the C-PC (PDB ID: 1GH0) was verified in its complete form (Full) or just its F chain with two pro-apoptotic proteins (p53- PDB ID: 1C26- and Bax- PDB ID: 1F16). The C-PC*

	does not interact with p53, only Bax in its two forms with binding energy of -1.54 (Full) and -21.97 (chain F). UCSF Chimera (program for the interactive visualization and analysis of molecular structures) revealed that the F chain was connected to Bax by two Hydrogen bonds and 180 varied connections (polar, nonpolar, favorable and unfavorable). In silico analyzes showed preferential interaction of C-PC with Bax, without any interaction with p53. The higher binding energy with the F chain in relation to the complete structure of C-PC indicates greater stability of the protein complex. The docking demonstrated the feasibility of carrying out in vitro and in vivo studies to assess the possible stimulatory role of C-PC on Bax.

Introduction

. *Apoptosis, programmed cell death, has an important role in maintaining tissue homeostasis in multicellular organisms* (1) *and pro-apoptotic proteins participate in this event. To coordinating the DNA damage response, p53 protein can induce apoptosis, performing a central role in the prevention of neoplastic transformation* (2). *Besides that, apoptosis can be stimulated by the insertion of Bax protein from the cytosol into mitochondrial membranes* (3). *Defects in the physiological mechanisms of apoptosis may contribute to different human diseases like cancer* (4). *One of these defects could be the downregulation of p53 and Bax, which end up becoming interesting therapeutic targets. The C-phycocyanin, photosynthetic pigment, has anti-tumor activities and could exert upregulation on pro-apoptotic proteins. Thus, the objective of this study was to verify the interaction between C-PC and two proapoptitic proteins: p53 and Bax.*

Materials and Methods

Proteins structures were obtained from Protein Data Bank (PDB) (5) *according PDB ID. For protein interaction verification we used the PRISM web server, (available on http://cosbi.ku.edu.tr/prism/) considering C-PC (PDB ID: 1GH0, in full structure or F chain only), tetramerization domain of p53 (PDB ID 1C26) and Bax (PDB ID 1F16). Each target was subjected to docking simulation with: 1- C-PC full structure and 2- only F chain totaling 4 docking simulations (we provided on the server PDB ID for each pair of proteins). The possible binding modes were generated by server (number of possible binding modes depending of pair analyzed) and only the most negative binding energy (greater stability) was showed in results. The binding mode with greater binding energy was analyzed with UCSF Chimera program (available to download at http://www.cgl.ucsf.edu/chimera/download.html).for verification of Hydrogen bonds and varied connections (polar, nonpolar, favorable and unfavorable).*

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Results and Discussion

There was no docking between CPC (full or F chain) with tetramerization domain of p53. With Bax protein, the two forms of C-PC obtained docking (Fig 1, A and B). The Bax-Full C-PC complex had a lower negative binding energy (-1.54) in relation to the Bax-F chain complex (-21.97 of binding

energy). A detailed analysis of the Bax-F chain complex was made and was verified the existence of two Hydrogen bonds between the molecules (Fig. 1C), as well as 180 varied connections (Fig. 1D). The more negative binding energy for the Bax-F chain complex indicates greater stability and affinity (6,7). *Besides that, the Hydrogen bonds established between the molecules must contribute to the biological effect of C-PC, because Hydrogen bonds profoundly influence the architecture and activity of biological macromolecules* (8).

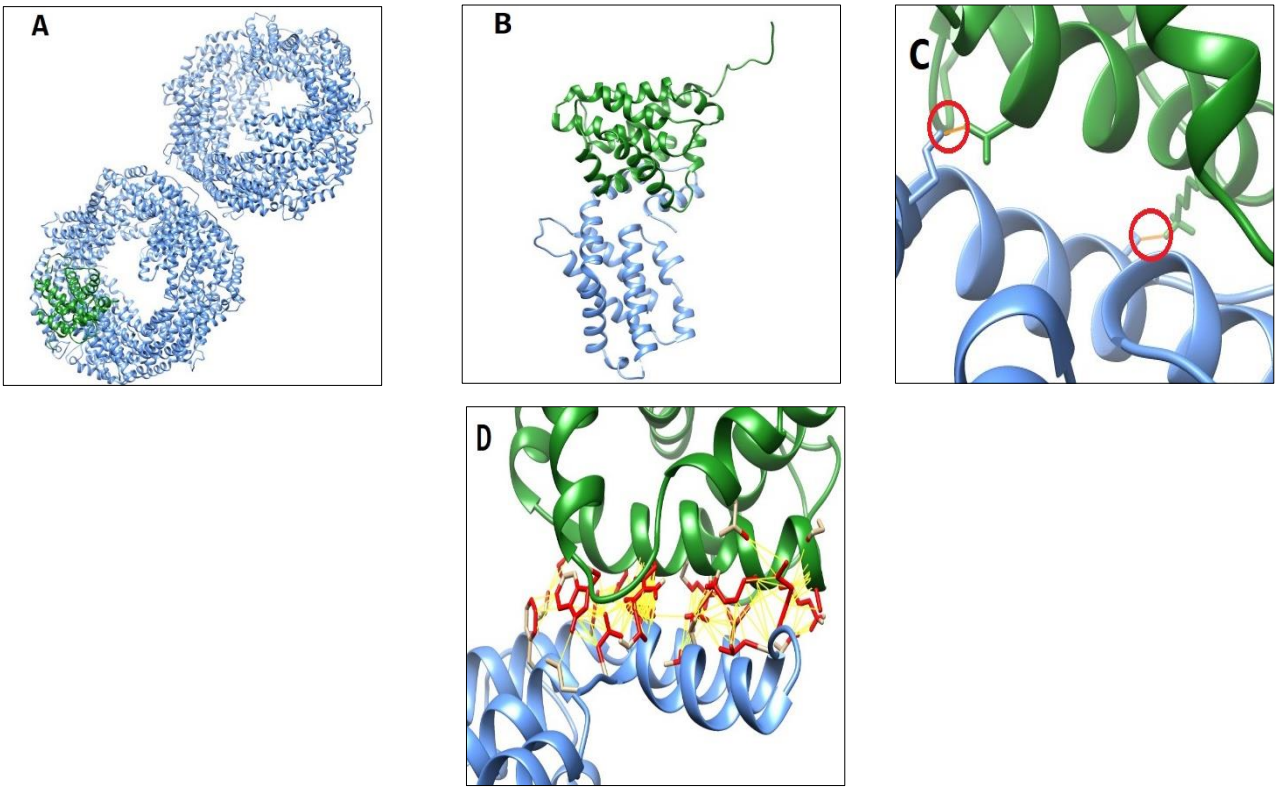

Figure 1: C-phycocyanin (C-PC in blue) and Bax protein (Green) interaction. Bax- Full C-PC complex (A); Bax- F chain complex (B); Hydrogen bonds (orange lines with red circle around) of Bax- F chain complex (C) and varied connections (polar, nonpolar, favorable and unfavorable) of Bax- F chain complex (D).

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Conclusions

In silico analyzes are valuable tools to assist in drug screening programs. In this study, docking revealed the feasibility of carrying out in vitro and in vivo studies to assess the possible stimulatory role of C-PC on Bax.

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