A007 **Structural Biology in the Fight Against Infectious Diseases**

The anti-influenza effect of flavonoids

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Influenza virus cause infection of upper respiratory tract which is responsible for 290 000-650 000 deaths annually [1]. Due to its high virulence and mutation rate, the influenza virus remains a major threat to public health even though vaccines are available. There are many targets for drug development within virus particle, one of them is RNA-polymerase (RdRp). Influenza RdRp is a heterotrimeric enzyme composed of three subunits PA (polymerase acidic protein), PB1 and PB2 (polymerase basic protein 1 and 2). Influenza RdRp is unable of synthesize the 5'mRNA cap required for translation and is forced to obtain it from host mRNA by "cap-snatching" mechanism. PA subunits play major role during this process as it has endonuclease activity. PA is binuclear protein subdivided into C-terminal and N-terminal domain (PA-Nter) connected by a long peptide chain. The active site localized at PA-Nter is negatively charged pocket with two divalent ions either Mn^{2+} or Mg^{2+}, which are critical for endonuclease activity. Inhibitors with possibility to tightly chelate these ions can block active site and thus interfere with its activity. Here, we report summary of possibility usage of diverse flavonoids and its analogs as inhibitors of PA endonuclease activity. IC_{50} of these compounds were characterized by AlphaScreen assay and Gel-based endonuclease assay. Also, three structures accompanying this summary of PA-Nter with orientin (PDB ID 7NUG) at 1.9 Å, quambalirine B (PDB ID 6YEM) at 2.5 Å and luteolin (PDB ID 6YA5) at 2.0 Å were solved [2,3].

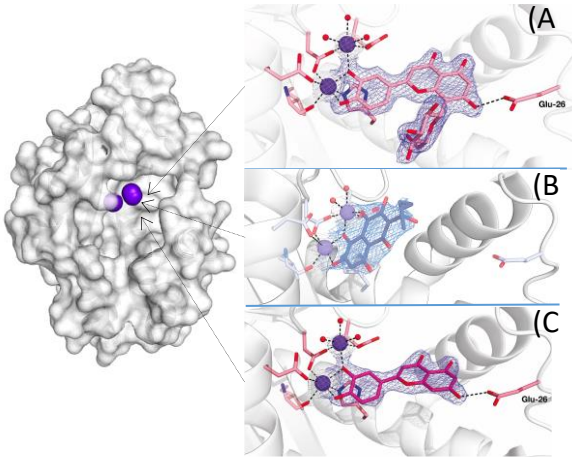

Figure 1. Crystal structures of PA-Nter in complex with orientin (**A**; PDB ID 7NUG), quambalirine B (**B**; PDB ID 6YEM) and luteolin (**C**; PDB ID 6YA5). The active site pocket containing two metal ions (purple spheres) is presented as a grey surface. Interacting residues and ligands are in stick representation. Hydrogen bonds are shown as black dashes. Coordinating water molecules are presented as red spheres [2,3].

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