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In silico study of African swine fever virus DNA Topoisomerase II and its inhibition by genistein

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African swine fever virus (ASFV) is the etiological agent of African swine fever: a lethal disease of pigs that has significant consequences for the pig industry in affected countries.

Viral targets for therapeutic influences against ASFV aren't studied yet. ASFV codes for a DNA Topoisomerase II (ASFV-TOPOII), which could be a possible target for treatment of the viral disease. Genistein is an isoflavone, which have significant antiviral activity against different viruses.

In order to reveal mechanisms of suppressing effect of genistein on ASFV-TOPOII in silico experiments on interaction of ASFV-TOPOII tertiary structure and genistein has been performed. Experiments include homology modeling, molecular docking and virtual ligand screening between ASFV-TOPOII model and genistein.

In order to obtain ASFV-TOPOII tertiary structure based on the structures of its close homologues has been performed homology modeling using ICM-PRO 3.8-7 program package with full refinement option in the ICM force field.

The crystal structure of ASFV-TOPOII dimer from Saccharomyces cerevisiae [PDB: 4GFH] was used as an object for evaluation. As a result of the protein-protein docking, 100000 models of the ASFV-TOPOII dimer structure were obtained. The model with the lowest interaction energy (-106.1 kcal/mol) and the lowest RMSD (8.974Å) in comparison with the 4GFH structure was chosen as the best one. The structure of the best obtained ASFV-TOPOII dimer model in the complex with four Mg^{2+} ions was solvated by a water shell 7 Å thick around it. The resulting system was subjected to 30,000 steps of a SD minimization algorithm and to 60,000 steps of ABNR minimization algorithm.

For docking analysis, were selected all 16 amino acids in the ATP-binding site as possible interaction sites with genistein. Docking of ATP and genistein with ASFV-TOPOII dimer model was conducted. The side chains of selected amino acids were flexible. As a result of 300 independent docking experiments, 3000 interaction models of ATP and genistein with ASFV-TOPOII dimer were obtained. The best models based on the smallest ICM score value and lowest binding energy were chosen. As a result of experiments, was shown that genistein formed hydrogen bonds with the ATP-binding site residues: Asn-144, Val-146, Gly-147 and Leu-148. Binding energy values revealed that genistein bound to the ATP-binding site with more affinity (-4.62 kcal/mol) as compared to ATP (-3.02 kcal/mol), suggesting that genistein could effectively compete with ATP for the binding site. The obtained results were also confirmed by in vitro experiments.

The following conclusions may be drawn from the results of our study:

1. In the ATP binding site genistein, compared to ATP, showed a high degree of interaction with ASFV-TOPOII, which could lead to inhibition of ASFV-TOPOII - ATP interaction.
2. The obtained results showed the possibility of using flavonoids as inhibitors of ASFV-TOPOII and possible therapeutic agent against ASFV.