Farnesoid X Receptor as a potential protein target for mushroom LMW compounds: virtual screening using molecular docking

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Farnesoid X receptor (FXR) is a nuclear receptor protein involved in controlling several metabolic pathways, with bile acids as his natural ligands. FXR functions as a sensor for bile acids, thus promoting their clearance by controlling expression of genes involved in bile acids transport and metabolism. FXR has been recently regarded as an important target for drug discovery and the research for small molecules, that modulates his interaction with binding co-regulator proteins, is ongoing. Very recently, several reports have shown natural compounds and extracts with activity as, either agonists or antagonists of FXR, notably steroids (1) and polyphenols (2). Mushrooms have been widely recognised as presenting in their chemical constitution polyphenols and steroids in significant amounts, either in quantity and diversity.

For this reason we set out to investigate FXR as a potential target for LMW compounds present in mushrooms. To meet this goal we virtually screened a database of 40 compounds, present in mushrooms, against a carefully prepared 3D crystal structure of FXR (PDB code: 1OIV). The molecular docking software used for this virtual screening project was AutoDock Vina (VINA) and the database of LMW compounds were revised and prepared by us. VINA presents the results as predΔG (predicted binding energy), with compounds with the lowest predΔG expected to be the ones with more potent FXR modulating activity.

Among the tested compounds, steroids presented the lowest predΔG, with several displaying values below -10 kcal/mol including: Ergosta-4,6,8(14),22-tetraen-3-one (-10,5 kcal/mol), Ganoderic acid A (-10,4 kcal/mol), Ganoderic acid A (-10,3 kcal/mol) and Ergosterol (-10,2 kcal/mol). These results are not unexpected, as FXR natural ligands are in fact bile acids, that belong to the steroid class of compounds. Also, the predΔG values of the top ranked steroids compared well with the predΔG value of a benzamide derivative compound (10,6 kcal/mol), a known inhibitor of FXR that is co-crystallized in the 1OIV crystal structure.

In conclusion, this initial study points to FXR as a potential target for mushroom compounds and extracts, especially steroid derivatives or extracts. Although further studies are needed to confirm this hypothesis, this work demonstrates the usefulness of using an *in silico* approach as a complement for experimental work.

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