

PharmMapper Server and Molecular Docking Study Focusing on Polydatin to Identify Potential Targets

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ABSTRACT

In this short communication, we focused on the biological role of Polydatin through two computerized analyzes (pharmacophore study by PharmMapper server and Molecular Docking by Autodock Vina with the Pyrx program). According to the best normalized fit scores calculated by the PharmMapper database, Polydatin may be attractive for the following potential targets: Triggering receptor expressed on myeloid cells 1; Ephrin type-B receptor; Tyrosine protein kinase (HCK); ADP -ribose pyrophosphatase; mitochondrial Putative ATP-dependent Clp protease proteolytic subunit; Seprase and Caspase-3, ranked by normalized fit score in descending order (0.9921 to 0.9812). All these potential targets calculated by PharmMapper server are used to evaluate their role by the Docking method through Autodock Vina with Polydatin. From the results of the binding energies of our docking approach, only three potential targets play a key role with Polydatin, which are: the Trigger receptor expressed on myeloid cells, mitochondrial ADP -ribose pyrophosphatase, and Seprase (fibroblast activation protein). However, further computational methods and *in vitro* and *in vivo* assays are required to confirm our preliminary results.

Keywords: Polydatin, Pharmacophore, Autodock Vina, Molecular Docking, PharmMapper

INTRODUCTION

Computational biology is nowadays focused on the design and development of computer models to represent and simulate biological systems and solve related problems. In recent years, these disciplines have attracted increasing interest in the medical field [1].

In biology and medicine, there are a number of computational methods aimed at reducing experimental times and costs in drug delivery and discovery. Among the most studied methods is Molecular Docking [2], a computational method required for structure-based virtual screening to identify new molecular candidates for the development of new therapeutic approaches. Another well-known investigation is Pharmacophore analysis [3], which is based on the spatial arrangement of features essential for a molecule to interact with a specific target receptor and is an alternative method to molecular docking to achieve this goal.

The focus of the present study was to use Autodock Vina to determine the best theoretical binding energies scores (kcal/mol) of Polydatin with various potential target proteins and receptors [4]. Other computational methods well known nowadays are the study of drug similarity assessment and ADMET (absorption, distribution, metabolism, excretion and toxicity) prediction to investigate the pharmacokinetic and toxic properties of drugs and small compounds [5].

In this short communication, we mainly focus on two classical methods as Pharmacophore and Molecular Docking studies focused on the biological role of the natural compound named Polydatin, a natural potent Polyphenol. Polydatin (PD), also called Piceid (3,4',5-trihydroxystilbene-3- β -d-glucoside), is a glycosylated form Resveratrol with excellent anticancer and antioxidant properties [6]. Many papers in the Literature reported that PD has antioxidant, anti-free radical, and anti-inflammatory properties [6-8].

MATERIALS AND METHODS

PharmMapper Server (<http://www.lilab-ecust.cn/>)

It is an open-access web server for identifying potential targets (drugs, natural products, or other newly discovered compounds with as yet unidentified binding targets) using the Pharmacophore mapping approach. Thank you to the highly efficient and robust mapping method, PharmMapper has a high throughput performance and can identify the potential targets from the database within a few hours [9].

Target Receptor Preparation for Docking Analysis

The 3D structures investigated in this work are:

Tiggering receptor expressed on myeloid cells 1 (PDB 1Q8M); Ephrin type-B receptor 4 (PDB 2VWU); Tyrosine protein kinase (PDB 2HCK); mitochondrial ADP-ribose Pyrophosphatase (PDB 1Q33); Seprase (PDB 1Z68); Caspase-3 (PDB 3DEJ). These targets are accurately prepared by Chimera program: all hydrogens and Gasteiger charges were added by Chimera and finally the structures were converted in PDBQT format.

Ligand Preparation Workflow for Docking Analysis

PD was taken from the PubChem Database (<https://pubchem.ncbi.nlm.nih.gov/>) in 3D Conformer SDF and was processed by Chimera through MFF94 force field with Steepest Descent Optimization Algorithm. All hydrogens and Gasteiger charges were added by Autodock Tools and finally the structures were minimized and converted in PDBQT format.

RESULTS AND DISCUSSION

PharmMapper Server

PharmMapper Server is a freely accessible web server designed to identify potential targets for given small probe molecules (drugs, natural products, or other newly discovered compounds with unidentified binding targets) using the Pharmacophore Mapping approach [9].

PharmMapper was used to test the potential target proteins for PD. This is one of the web servers for potential drug targets identification via the large-scale reverse pharmacophore mapping strategy. Drug target identification, which involves several different algorithms for finding genes and proteins, is the first step in drug discovery. When 3D structures of the targets are available, the problem of target identification is usually transferred to finding the best mode of interaction between the potential target candidates and the small molecule probes. Pharmacophore is the spatial arrangement of features essential for a molecule to interact with a particular target receptor, and was applied as a preliminary evaluation of the target molecules before molecular docking analysis. The best results from PharmMapper analyses are reported in Table 1.

Table 1: Best Pharmacophore candidates of Polydatin, identified by PharmMapper

PDB ID	Target name	Normalized fit score
1Q8M	Triggering Receptor	0.9921
2VWU	Ephrin type-B receptor 4	0.9887
2HCK	Tyrosine protein kinase	0.9877
1Q33	mitochondrial ADP-ribose pyrophosphatase	0.9843
1Z68	Seprase	0.9843
3DEJ	Caspase-3	0.9812

The characteristics of the selected targets are briefly reported below.

PDB 1Q8M (Crystal Structure of the Human Myeloid Cell Activating Receptor TREM-1):

Triggering receptors expressed on myeloid cells (TREM) are a family of recently discovered receptors that play an important role in innate immuno responses, such as activation of inflammatory responses and septic shock in response to microbially mediated infections.

PDB 2VWU (EphB4 Kinase Domain Inhibitor Complex):

The EphB4 is one of the Eph receptor family, the largest subgroup of tyrosine kinase receptors, associated with angiogenesis, growth, and metastasis of tumors, making it a valuable and attractive target for drug development for therapeutic applications.

PDB 2HCK (SRC FAMILY KINASE HCK-QUERCETIN COMPLEX):

Hematopoietic cell kinase (HCK) is a member of the SRC family of cytoplasmic tyrosine kinases (SFKs), involved in diverse inflammatory responses.

PDB 1Q33 (Crystal Structure of Human ADP-ribose pyrophosphatase NUDT9):

The human ADP-ribose pyrophosphatase NUDT9 belongs to a superfamily of Nudix hydrolases that degrade potentially toxic compounds in the cell. The enzyme hydrolyzes ADP-ribose (ADPR) to AMP and ribose 5'-phosphate. NUDT9 has 39% sequence similarity with the C-terminal

cytoplasmic domain of the ADPR-gated calcium channel TRPM2, which has low but specific enzyme activity.

PDB 1Z68 (Crystal Structure of Human Fibroblast Activation Protein alpha):

The fibroblast activation protein alpha (FAPalpha), also called Seprase, is highly expressed in epithelial carcinomas and is involved in extracellular matrix remodeling, tumor growth, and metastasis.

PDB 3DEJ (Crystal Structures of Caspase-3 with Bound Isoquinoline-1,3,4-trione Derivative Inhibitors):

Caspase-3 is an attractive therapeutic target for the treatment of diseases in which apoptosis is involved.

Molecular Docking Analysis

These targets were further evaluated by the Molecular Docking analysis to confirm their binding affinity with PD. In Table 2 are shown the results of the Molecular Docking analysis with PD, compared with the results obtained with the relative crystal ligands reported in the PDB database.

Table 2: Binding Energy results from Molecular Docking analysis obtained from Autodock Vina, via Pyrx program

PDB ID	Target name	Binding Energy with Polydatin (kcal mol ⁻¹)	Binding Energy of Crystal ligands (kcal mol ⁻¹)
1Q8M	Triggering Receptor	-4.7	Glutathione (GSH): -3.7
2VWU	Ephrin type-B receptor 4	-8.6	tx1*: -9.0
2HCK	Tyrosine protein kinase	-9.2	Quercetin (QUE): -8-8
1Q33	mitochondrial ADP-ribose pyrophosphatase	-7.0	beta-D-glucopyranose (BGC): -5.9
1Z68	Seprase	-8.5	N.D.
3DEJ	Caspase-3	-7.4	RXC**: -7.7

* N-(5-chloro-1,3-benzodioxol-4-yl)-6-methoxy-7-(3-piperidin-1-ylpropoxy) quinazolin-4-amine

** (1S)-1-(3-chlorophenyl)-2-oxo-2-[(1,3,4-trioxo-1,2,3,4-tetrahydroisoquinolin-5-yl) amino] ethyl acetate

CONCLUSION

In this short communication, Polydatin, a natural compound, is tested with the PharmMapper server to identify its potential targets using the Pharmacophore Mapping approach. Then, the best protein and receptor targets identified were further evaluated by Molecular Docking analysis with Polydatin using the Autodock Vina algorithm. Our studies revealed that Polydatin could play a key role for the Trigger receptor on myeloid cells, ADP-ribose pyrophosphatase mitochondrial and Seprase (fibroblast activation protein). However, further computational analysis and *in vitro* and *in vivo* studies are needed to confirm these preliminary results. In addition, Polydatin may be a promising candidate in the regulation of Tyrosine kinase expression, although several experiments are required to reach this final conclusion.

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