Communication

Polydatin against HIV Proteases

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Abstract: Introduction: HIV (human immunodeficiency virus) is a virus that attacks and destroys one type of white blood cell, in particular, the CD4 lymphocytes, which are responsible for the body's immune response. This weakens the immune system to such an extent that it can no longer fight other viruses, bacteria, protozoa, fungi, and tumors. Methods: We investigated the potential biological role of the natural compound Polydatin (or piceid) using SwissDock, a web service to predict the molecular interactions that can occur between a target protein and a small molecule. Discussion: For the first time, we have investigated the role of polydatin against HIV-1 protease and HIV-2 protease through a computational approach by comparing their estimated ΔG values (kcal/mol) and the nature of the interactions between the residues in the catalytic center of the HIV proteases. Conclusion: From these simulations, Polydatin has excellent physical properties and an excellent estimated ΔG value (kcal/mol) of about -9.9 kcal/mol against HIV-2 protease and ΔG value (kcal/mol) of about -9.5 kcal/mol against HIV-1 protease. In addition, Polydatin was able to bind to two key amino acids of the catalytic triad sequence common to asparagine proteases (Asp25 and Gly27)

Keywords: polydatin; HIV; docking method; SWISS Dock Server

1. Introduction

The human immunodeficiency virus (HIV), which causes AIDS, is spread differently from country to country[1-4]. According to the World Health Organisation (WHO), around 40.1 million people have died from HIV/AIDS by 2021 and around 38.4 million people are infected with HIV worldwide [5].This study investigates the relationship between HIV-1 Protease and or HIV-2 Protease with the natural compound Polydatin (called Piceid), a natural precursor and glycoside form of resveratrol with a monocrystalline structure [6]. Figure1 shows its 2D and its 3D crystal structure. It is isolated from the bark of Picea sitchensis or Polygonum cuspidatum, polydatin may be detected in grape, peanut, hop cones, red wines, hop pellets, cocoa-containing products, chocolate products, and many daily diets [6].The detailed structure of the HIV protease has been used to design effective drugs for the treatment of AIDS [1;3]. HIV-2 is a virus of the Retroviridae family, Lentivirus genus; it represents one of the two HIV serotypes, together with the much more widespread HIV-1, which is responsible for the HIV pandemic worldwide. HIV-2, on the other hand, has a more limited geographic spread [7]. Figure 2 shows the comparison of the 3D crystal structures of HIV-1 protease and HIV-2 protease with their crystal inhibitors in the active site. The focus of this work was to evaluate, using computational methods, the potential biological role of these HIV proteases with polydatin. We chose to investigate Piceid because many scientific articles report not only that it has low side effects [6] compared to other natural substances but also because it has different biological properties, for example, antioxidant [8], anti-inflammatory [9], and anticancer properties [10]. In addition, polydatin has powerful anti-free radical activity [8], and it reduces oxidative stress on cells and tissues [11].
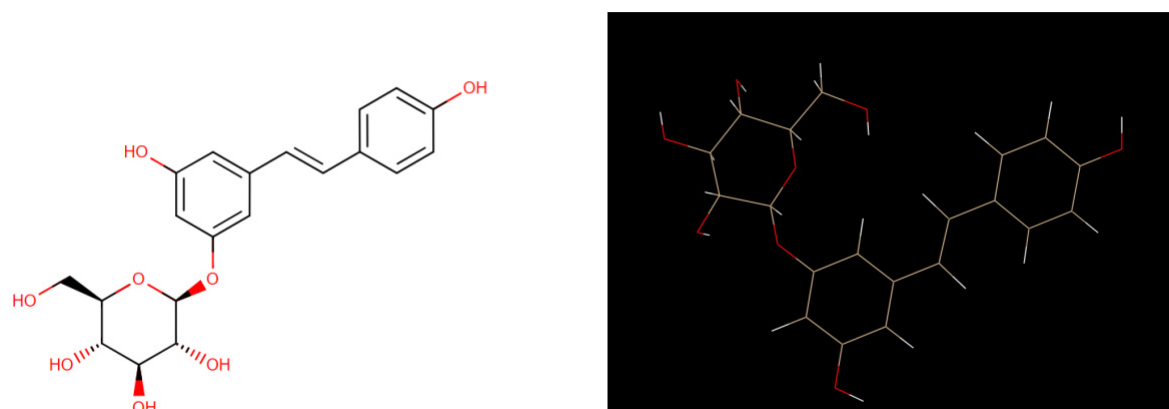
Figure 1. Comparison of 2D   Crystal structure and 3D structure of Polydatin The figure was reproduced by   Drug Bank Database and UCSF Chimera   program.
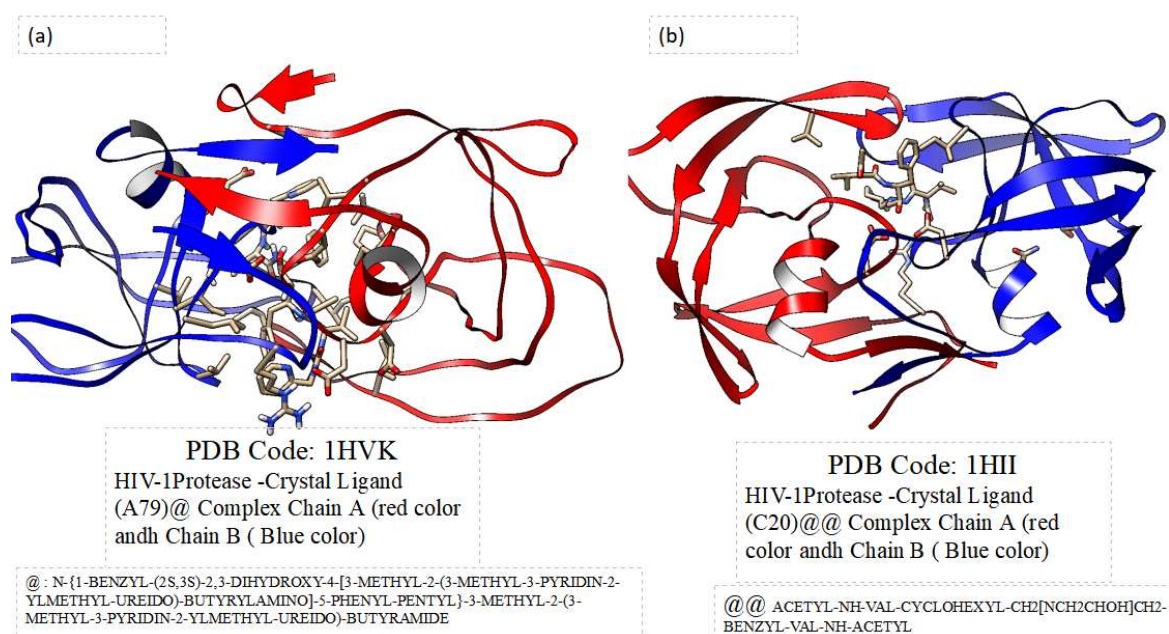

(a)

(b)

PDB Code: 1HVK
HIV-1Protease -Crystal Ligand
(A79)@ Complex Chain A (red color
andh Chain B (Blue color)

PDB Code: 1HII
HIV-1Protease -Crystal Ligand
(C20)@@ Complex Chain A (red
color andh Chain B (Blue color)

@ : N-{1-BENZYL-(2S,3S)-2,3-DIHYDROXY-4-[3-METHYL-2-(3-METHYL-3-PYRIDIN-2-
YLMETHYL-UREIDO)-BUTYRYLAMINO]-5-PHENYL-PENTYL}-3-METHYL-2-(3-
METHYL-3-PYRIDIN-2-YLMETHYL-UREIDO)-BUTYRAMIDE

@@ ACETYL-NH-VAL-CYCLOHEXYL-CH2[NCH2CHOH]CH2-
BENZYL-VAL-NH-ACETYL

Figure 2. 3D Crystal structures of HIV-1 protease and HIV-2 protease with their crystal inhibithor in the Active site. The figure was reproduces by UCSF Chimera   program. Crystal structures were taken by Protein Data Bank (PDB code: 1hvk and PDB code: 1hii).

2. Material and Methods

SwissDock, a web service for predicting molecular interactions that might occur between a target protein and a small molecule [12], was used to predict the potential role of Polydatin with HIV-1 protease and HIV-2 protease. SwissDock and S3DB are developed by Aurélien Grosdidier, Vincent Zoete and Olivier Michielin, from the Molecular Modeling Group of the Swiss Institute of Bioinformatics in Lausanne, Switzerland[12]. SwissDock is based on the docking software EADock DSS, whose algorithm consists of the following steps[12]:

- many binding modes are generated either in a box (local docking) or in the vicinity of all target cavities (blind docking).

-simultaneously, their CHARMM energies are estimated on a grid.

-the binding modes with the most favorable energies are evaluated with FACTS, and clustered.

-the most favorable clusters can be visualized online and downloaded on your computer.

In this wok, 3D Crystal structures of HIV-1 protease and HIV-2 protease with their crystal inhibithor in the Active site and saved in PDB format .Crystal structures were taken by Protein Data Bank (PDB code: 1hvk and PDB code: 1hii). Polydatin was downloaded from Pubchem Database and saved in SDF format.

3. Results and Discussion

For the first time, this theoretical study focused on the relation between HIV-1 protease and HIV-2 protease with a natural compound named polydatin (or Piceid, 3,4,5-trihydroxystilbene-3-beta-monoglucoside). Several papers have reported the excellent biological role of this compound in the literature [8,11]. However, there are few recent works that have studied the role of polydatin in the HIV virus [13, 14]. Heredia et al. 2020 reported synergistic inhibition of HIV-1 in activated and remaining peripheral blood mononuclear cells, monocyte-derived macrophages, and selected drug-resistant isolates with nucleoside analogs combined with a natural product, resveratrol [13]. Pflieger et al. (2013 studied natural stilbenoids isolated from grapevine exhibiting inhibitory effects against HIV-1 integration and eukaryote MOS1 transposase in vitro activities [14].

Our main contribution was to investigate polydatin by molecular docking with HIV-1 protease and HIV-2 protease, respectively. The methods were performed by SwissDock Server, a web service for predicting molecular interactions that might occur between a target protein and a small molecule [12]

Table 1. shows the   comparison   docking results evaluated by SwissDock. As can be seen from this Table, Polydatin has been shown to have a higher estimated ΔG score   than the ligand crystal both in the case of HIV-2 protease and HIV-1 : (Estimated ΔG   of   Polydatin was -9.89 kcal/mol   VS Estimated   ΔG   of   Crystal   Ligand   C20   [ACETYL-NH-VAL-CYCLOHEXYL-CH2[NCH2CHOH]CH2-BENZYL-VAL-NH-ACETYL) was -12.14 kcal/mol, when they binds in the acitive site of HIV-2, while Estimated ΔG   of   Polydatin was -9.47   kcal/mol VS Estimated ΔG   of Crystal   ligand   A79   (N-{1-BENZYL-(2S,3S)-2,3-DIHYDROXY-4-[3-METHYL-2-(3-METHYL-3-PYRIDIN-2-YLMETHYL-UREIDO)-BUTYRYLAMINO]-5-PHENYL-PENTYL}-3-METHYL-2-(3-METHYL-3-PYRIDIN-2-YLMETHYL-UREIDO)-BUTYRAMIDE) was -12.54 kcal/mol, when they binds in the acitive site of HIV-1 protease. However, a very important aspect that we noticed was the binding ability of Polydatin when it binds to HIV-1 protease or HIV-2 protease is not the same.

In fact, if we observe the respective estimated ΔG scores , it can be seen that Polydatin shows a greater ability to bind with HIV-2 protease compared to when it binds with HIV-1 protease (excellent low ΔG score of -9.89 kcal/mol of ΔG when Polydatin binds with HIV-2 protease ; VS a good ΔG score of -9.47 kcal/mol of ΔG , when Polydatin binds with   HIV-1 protease.

These results are significant not only because they demonstrate the ability of polydatin to bind better with HIV-2 protease compared to when it binds with HIV-1 protease, even though they have a 54% similar sequence between them [15], but also because the polydatin in the active site of these proteases could bind to two key amino acids of the catalytic triad sequence common to aspartic proteases (Asp25 and Gly27; see below Figure 4 and Figure 6).

In Figure 3 and Figure 4, we reported the 3D structure of HIV-1 protease with crystal ligand A79 and polydatin complex, respectively, and the 2D diagrams that occur between HIV-1 protease amino acid residues and atoms in crystal ligand A79 and polydatin, respectively.

In Figure 5 and 6, we reported the 3D structure of HIV-2 protease with crystal ligand C20 and polydatin complex, respectively, and the 2D diagrams that occur between HIV-2 protease amino acid residues and atoms in crystal ligand C20 and polydatin, respectively.
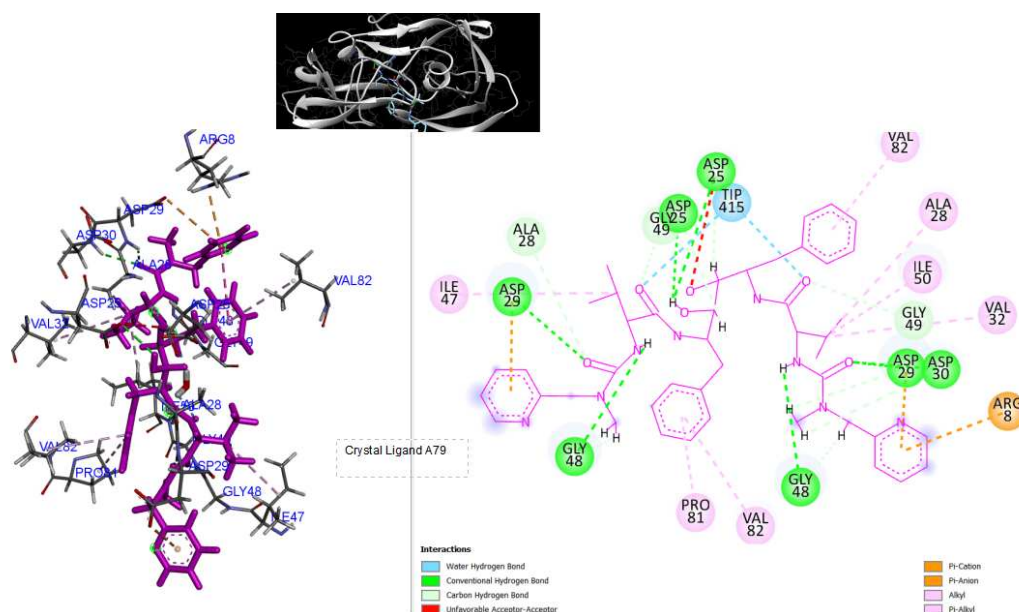
Figure 3. 3D Crystal structures of HIV-1 protease   and 2D Diagrams residues interactions that occur between HIV-1 protease amino acid residues and atoms in   crystal ligand   A79:   [N-{1-BENZYL-(2S,3S)-2,3-DIHYDROXY-4-[3-METHYL-2-(3-METHYL-3-PYRIDIN-2-YLMETHYL-UREIDO)-BUTYRYLAMINO]-5-PHENYL-PENTYL}-3-METHYL-2-(3-METHYL-3-PYRIDIN-2-YLMETHYL-UREIDO)-BUTYRAMIDE]in the Active site. The figure was reproduced by Discovery Studio Biovia Visualizer   program. Crystal structure was taken by Protein Data Bank (PDB code: 1hvk).

Figure 4. 3D Crystal structures of HIV-1 protease and   2D Diagrams residues interactions that occur between HIV-1 protease amino acid residues and atoms in Polydatin   in the Active site. The figure was reproduced by Discovery Studio Biovia Visualizer   program. Crystal structure was taken by Protein Data Bank (PDB code: 1hvk).

Figure 5. 3D Crystal structures of HIV-2 protease and 2D Diagrams residues interactions that occur between HIV-2 protease amino acid residues and atoms in Cystal Ligand C20 [ACETYL-NH-VAL-CYCLOHEXYL-CH2[NCH2CHOH]CH2-BENZYL-VAL-NH-ACETYL)] in the Active site. The figure was reproduced by Discovery Studio Biovia Visualizer program. Crystal structure was taken by Protein Data Bank (PDB code: 1HII).
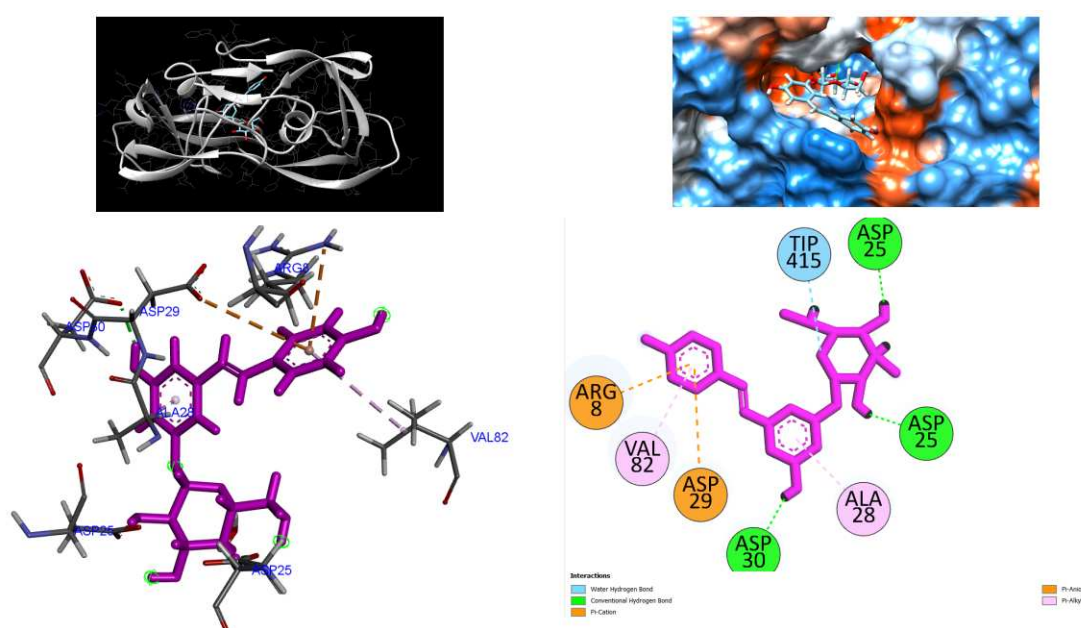

Figure 6. 3D Crystal structures of HIV-2 protease and 2D Diagrams residues interactions that occur between HIV-2 protease amino acid residues and atoms in Polydatin in the Active site. The figure was reproduced by Discovery Studio Biovia Visualizer program. Crystal structure was taken by Protein Data Bank (PDB code: 1HII).
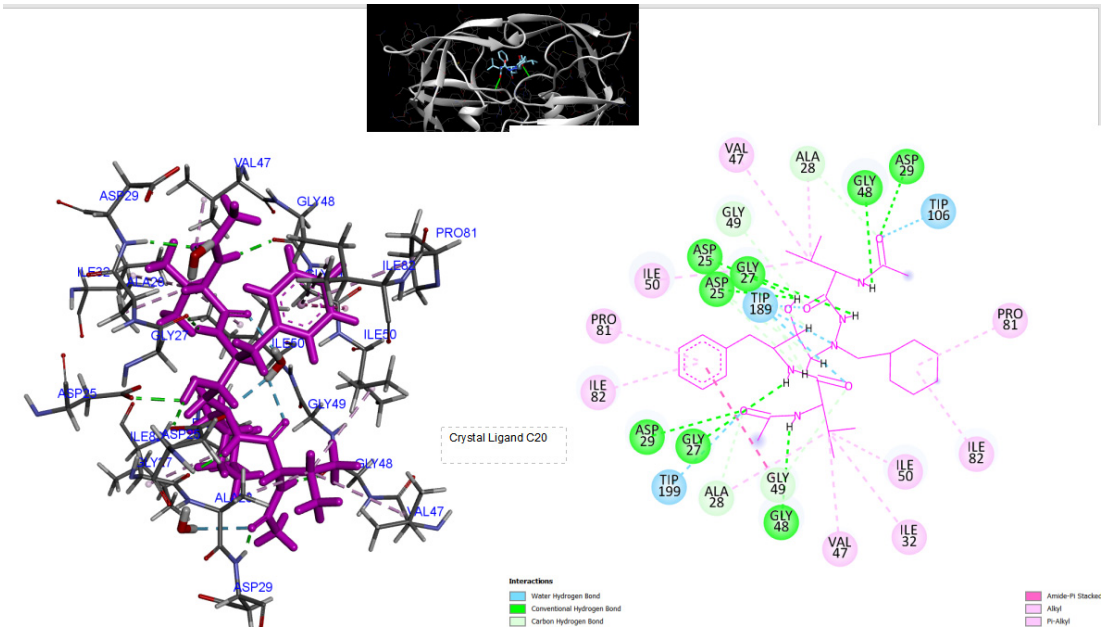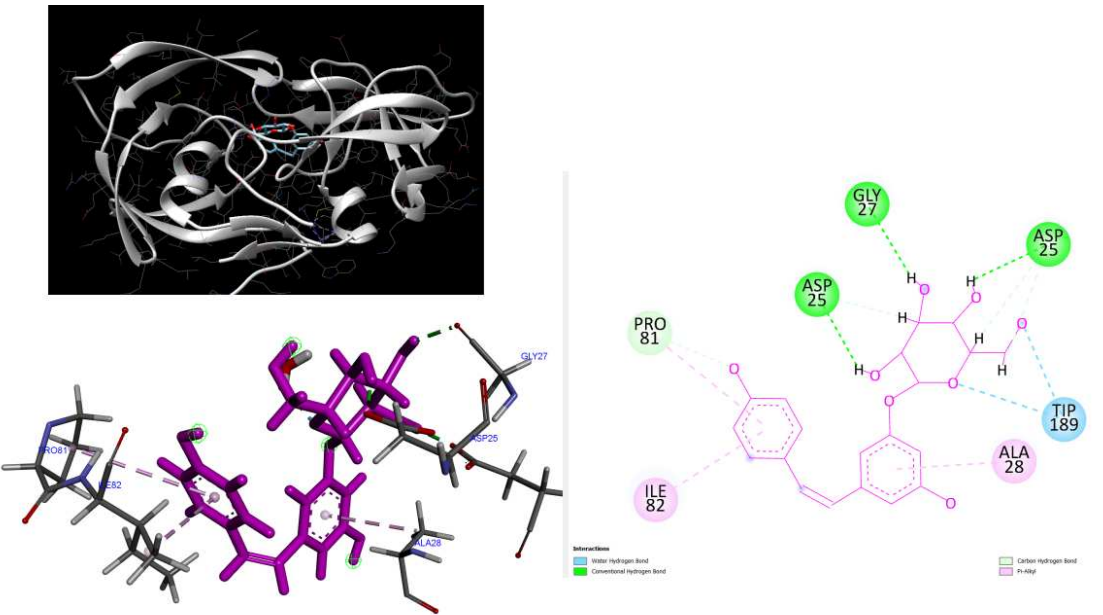
Table 1. Comparison Docking results of Polydatin and crystal ligands respectively, when they are complexed in HIV-1 protease or in HIV-2 protease respectively. The results were performed by SWISS Dock Service.

PDB	Target	Compound	FullFitness (kcal/mol)	Estimated ΔG (kcal/mol)
1HII	**HIV-2 PROTEASE**	**Polydatin**	**-780.51**	**-9.89**
1HVK	**HIV-1 PROTEASE**	**Polydatin**	**-770.76**	**-9.47**
1HII	HIV-2 PROTEASE	Crystal Ligand C20	-814.83	-12.14
1HVK	HIV-1 PROTEASE	Crystal Ligand A79	-822.14	-12.54

4. Conclussion

This short theoretical communication focused on the detection of the biological compound polydatin with HIV-1 protease or HIV-2 protease.
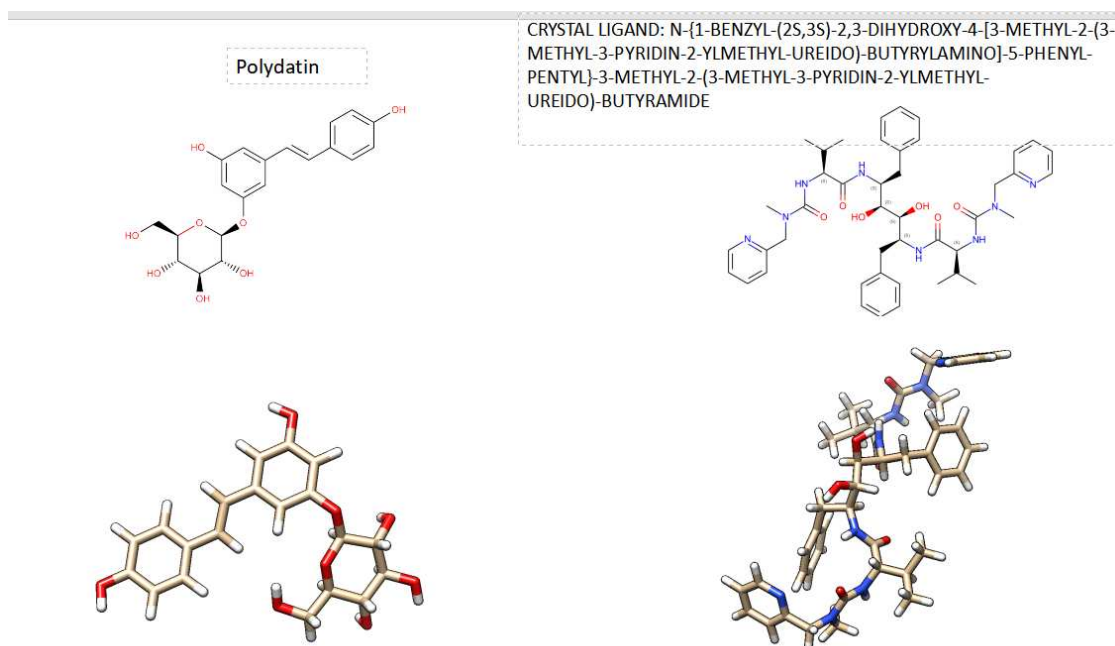
The method evaluated for this goal was the molecular docking approach, investigated by SWISS Dock. From these results, polydatin seems to demonstrate a greater ability to bond with HIV-2 protease than it does with HIV-1 protease. Indeed, comparing the estimated ΔG of polydatin with HIV-2, it was reported at -9.9 kcal/mol versus ΔG of polydatin-9.5 kcal/molwith HIV-1.

These computational results are very promising, although in vitro and in vivo studies are necessary to confirm our findings. When comparing the estimated ΔG of polydatin to HIV-2, a value of -9.9 kcal/mol was found, compared to a ΔG of polydatin of -9.5 kcal/mol for HIV-1. However, it is potentially able to bind well with both HIV proteases and be an effective inhibitor. An important aspect that we would like to emphasise is that polydatin, a polyphenol derivative of resveratrol, is a natural molecule that has few side effects compared to other natural substances, drugs or chemical substances. This aspect is very interesting because if in vitro and in vivo tests confirm that it is indeed able to block HIV, it could be an excellent strategy for both treatment and use, as it has no major side effects.

Supporting Information

PDB Code : 1HVK

HIV-1 PROTEASE-Crystal Ligand A79 COMPLEX (N-{1-BENZYL-(2S,3S)-2,3-DIHYDROXY-4-[3-METHYL-2-(3-METHYL-3-PYRIDIN-2-YLMETHYL-UREIDO)-BUTYRYLAMINO]-5-PHENYL-PENTYL}-3-METHYL-2-(3-METHYL-3-PYRIDIN-2-YLMETHYL-UREIDO)-BUTYRAMIDE)

SP Figure 1. Comparison 2D and 3D structures of Polydatin and Crystal Ligand A79 COMPLEX (N-{1-BENZYL-(2S,3S)-2,3-DIHYDROXY-4-[3-METHYL-2-(3-METHYL-3-PYRIDIN-2-YLMETHYL-UREIDO)-BUTYRYLAMINO]-5-PHENYL-PENTYL}-3-METHYL-2-(3-METHYL-3-PYRIDIN-2-YLMETHYL-UREIDO)-BUTYRAMIDE.

PDB Code : 1HII

HIV-2 PROTEASE-Crystal Ligand C20 COMPLEX (ACETYL-NH-VAL-CYCLOHEXYL-CH2[NCH2CHOH]CH2-BENZYL-VAL-NH-ACETYL)

SP Figure 2. Comparison 2D and 3D structures of Polydatin and Crystal Ligand C20 COMPLEX (ACETYL-NH-VAL-CYCLOHEXYL-CH2[NCH2CHOH]CH2-BENZYL-VAL-NH-ACETYL).

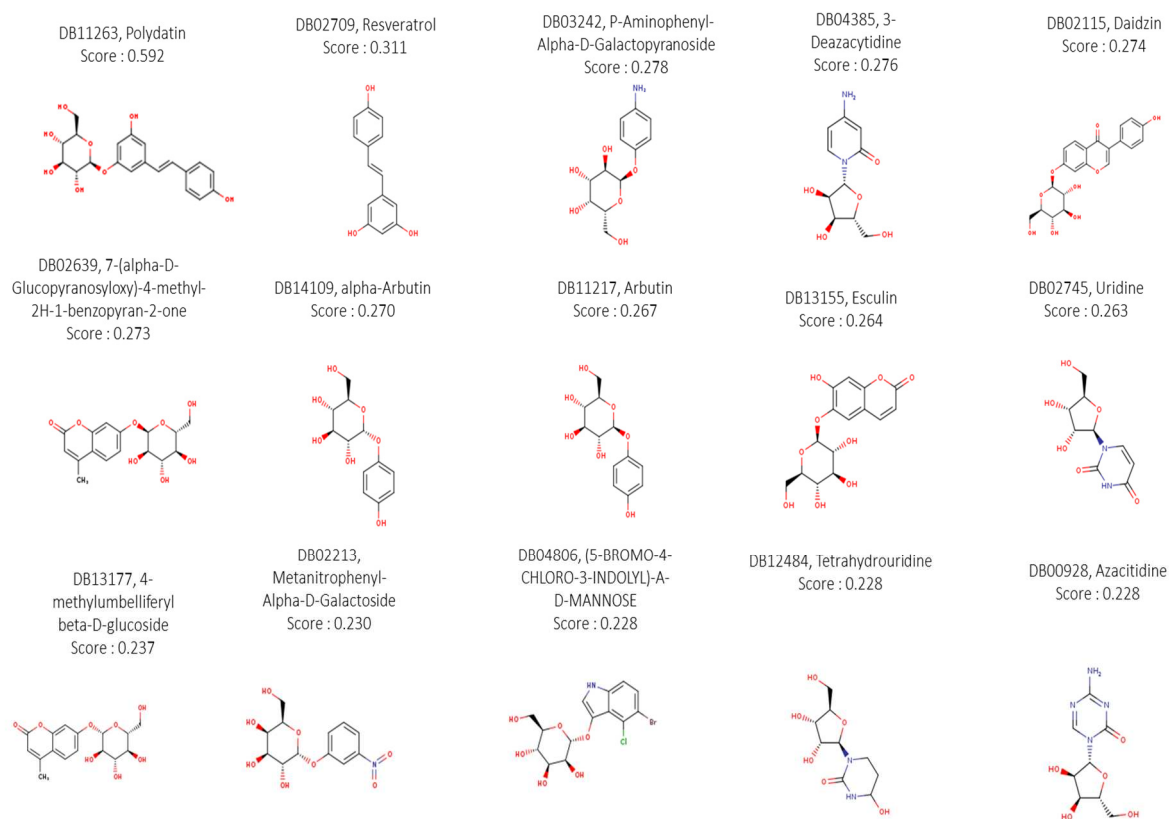| DrugBank ID	Similarity Score	Usual Name
DB11263	0.592	Polydatin
DB02709	0.311	Resveratrol
DB03242	0.278	P-Aminophenyl-Alpha-D-Galactopyranoside
DB04385	0.276	3-Deazacytidine
DB02115	0.274	Daidzin
DB02639	0.273	7-(alpha-D-Glucopyranosyloxy)-4-methyl-2H-1-benzopyran-2-one
DB14109	0.270	alpha-Arbutin
DB11217	0.267	Arbutin
DB13155	0.264	Esculin
DB02745	0.263	Uridine
DB13177	0.237	4-methylumbelliferyl beta-D-glucoside
DB02213	0.230	Metanitrophenyl-Alpha-D-Galactoside
DB04806	0.228	(5-BROMO-4-CHLORO-3-INDOLYL)-A-D-MANNOSE
DB12484	0.228	Tetrahydrouridine
DB00928	0.228	Azacitidine

SP Figure 3. Comparison Similary Scores performed by SWISS Similary web tool and Drug Bank.

SP Figure 4. Comparison 2D Structures were evaluated by Drug Bank through SWISS Similary web tool.

SMILES   OCC1OC(Oc2cc(C=Cc3ccc(cc3)O)cc(c2)O)C(C(C1O)O)O

Physicochemical Properties	
Formula	$C_{20}H_{22}O_8$
Molecular weight	390.38 g/mol
Num. heavy atoms	28
Num. arom. heavy atoms	12
Fraction Csp3	0.30
Num. rotatable bonds	5
Num. H-bond acceptors	8
Num. H-bond donors	6
Molar Refractivity	100.00
TPSA	139.84 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.75
Log $P_{o/w}$ (XLOGP3)	1.03
Log $P_{o/w}$ (WLOGP)	0.23
Log $P_{o/w}$ (MLOGP)	-0.36
Log $P_{o/w}$ (SILICOS-IT)	0.47
Consensus Log $P_{o/w}$	0.62

Water Solubility	
Log S (ESOL)	-2.90
Solubility	4.96e-01 mg/ml ; 1.27e-03 mol/l
Class	Soluble
Log S (Ali)	-3.56
Solubility	1.08e-01 mg/ml ; 2.78e-04 mol/l
Class	Soluble
Log S (SILICOS-IT)	-1.61
Solubility	9.67e+00 mg/ml ; 2.48e-02 mol/l
Class	Soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-7.95 cm/s

Druglikeness	
Lipinski	Yes; 1 violation: NHorOH>5
Ghose	Yes
Veber	Yes
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 1 violation: H-don>5
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: stilbene
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	4.82

SP Figure 5. Comparison chemical-physical, biological properties of Polydatin were performed by Swiss ADME web tool.

SwissTargetPrediction

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
Aldose reductase (by homology)	AKR1B1	P15121	CHEMBL1900	Enzyme	0.11573667475	37 / 15
Tyrosinase	TYR	P14679	CHEMBL1973	Oxidoreductase	0.11573667475	15 / 14
Sodium/glucose cotransporter 1	SLC5A1	P13866	CHEMBL4979	Electrochemical transporter	0.11573667475	59 / 26
Adenosine A2a receptor (by homology)	ADORA2A	P29274	CHEMBL251	Family A G protein-coupled receptor	0.11573667475	134 / 0
Sodium/glucose cotransporter 2	SLC5A2	P31639	CHEMBL3884	Electrochemical transporter	0.11573667475	196 / 44
Matrix metalloproteinase 1	MMP1	P03956	CHEMBL332	Protease	0.11573667475	11 / 0
Matrix metalloproteinase 7	MMP7	P09237	CHEMBL4073	Protease	0.11573667475	3 / 0
Matrix metalloproteinase 8	MMP8	P22894	CHEMBL4588	Protease	0.11573667475	10 / 0
Adenosine A3 receptor	ADORA3	P0DMS8	CHEMBL256	Family A G protein-coupled receptor	0.11573667475	104 / 0
Low affinity sodium-glucose cotransporter	SLC5A4	Q9NY91	CHEMBL1770047	Electrochemical transporter	0.11573667475	4 / 5
Cyclooxygenase-2	PTGS2	P35354	CHEMBL230	Oxidoreductase	0.11573667475	2 / 3
Equilibrative nucleoside transporter 1	SLC29A1	Q99808	CHEMBL1997	Electrochemical transporter	0.11573667475	75 / 0
DNA topoisomerase I	TOP1	P11387	CHEMBL1781	Isomerase	0.11573667475	28 / 0
Insulin-like growth factor binding protein 3	IGFBP3	P17936	CHEMBL3997	Secreted protein	0.11573667475	22 / 0
Purine nucleoside phosphorylase	PNP	P00491	CHEMBL4338	Enzyme	0.0	21 / 0

SP Figure 6. Comparison potential targets of Polydatin were performed by Swiss Target prediction web tool.

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