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Short Communication

# Prediction of the Potential Role of Polydatin against HIV-1 Protease and HIV-2 Protease by SWISSDock Server

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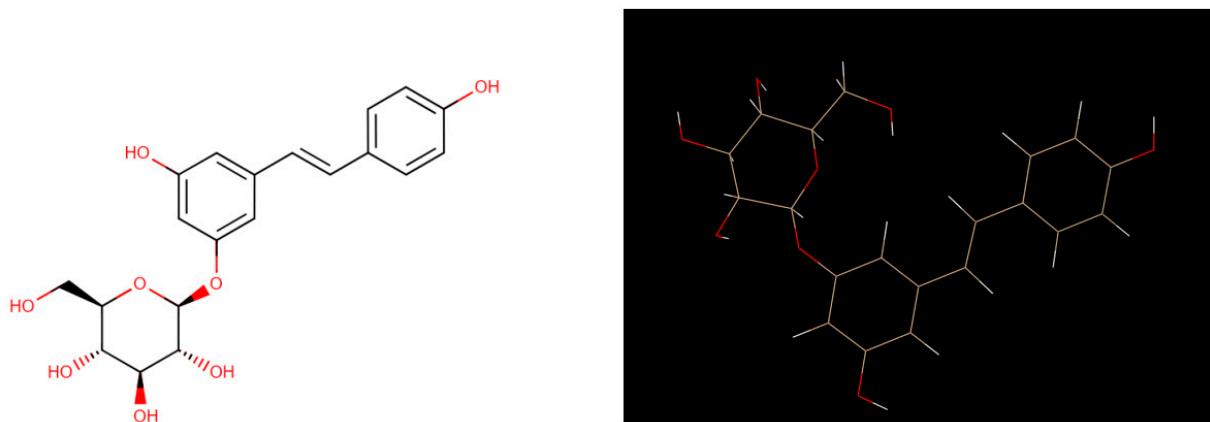
**Abstract:** Summary— Introduction: HIV (human immunodeficiency virus) is a virus that attacks and destroys one type of white blood cell in particular, the CD4 lymphocytes, which are responsible for the body's immune response. This weakens the immune system to such an extent that it can no longer fight other viruses, bacteria, protozoa, fungi and tumours. 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  $\Delta G$  values (kcal/mol) and the nature of the interactions between the residues in the catalytic centre of the HIV proteases. Conclusion: From these simulations, Polydatin has excellent physical properties and an excellent estimated  $\Delta G$  value (kcal/mol) of about -9.9 kcal/mol against HIV-2 protease and  $\Delta G$  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

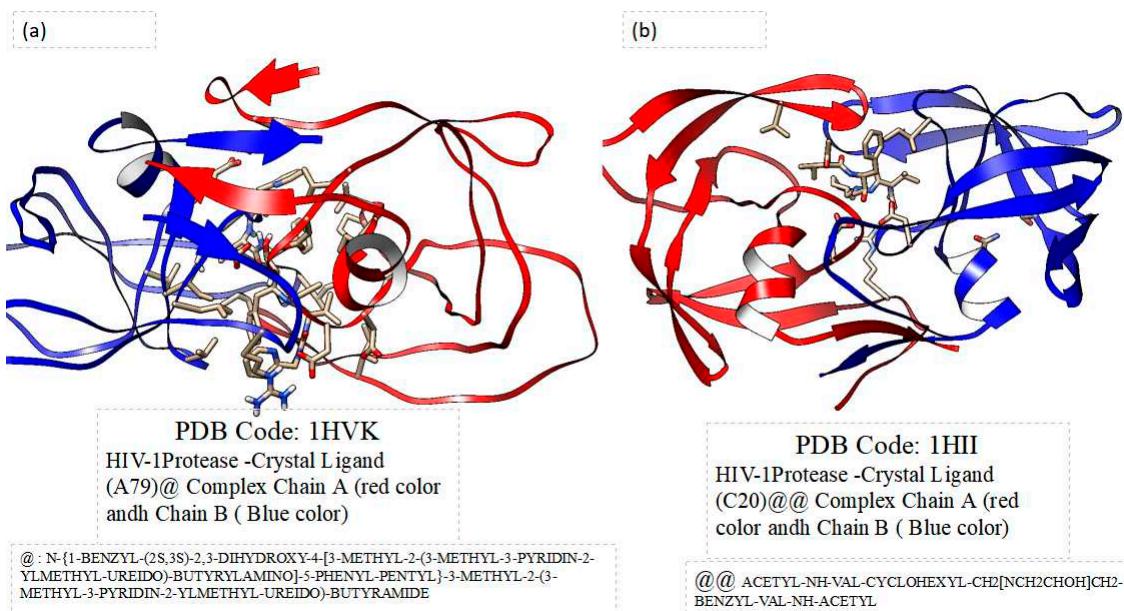
## 1. Introduction

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]. Figure 1 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 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.



**Figure 2.** 3D Crystal structures of HIV-1 protease and HIV-2 protease with their crystal inhibitor in the Active site. The figure was reproduced 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 Michelin](#), 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.

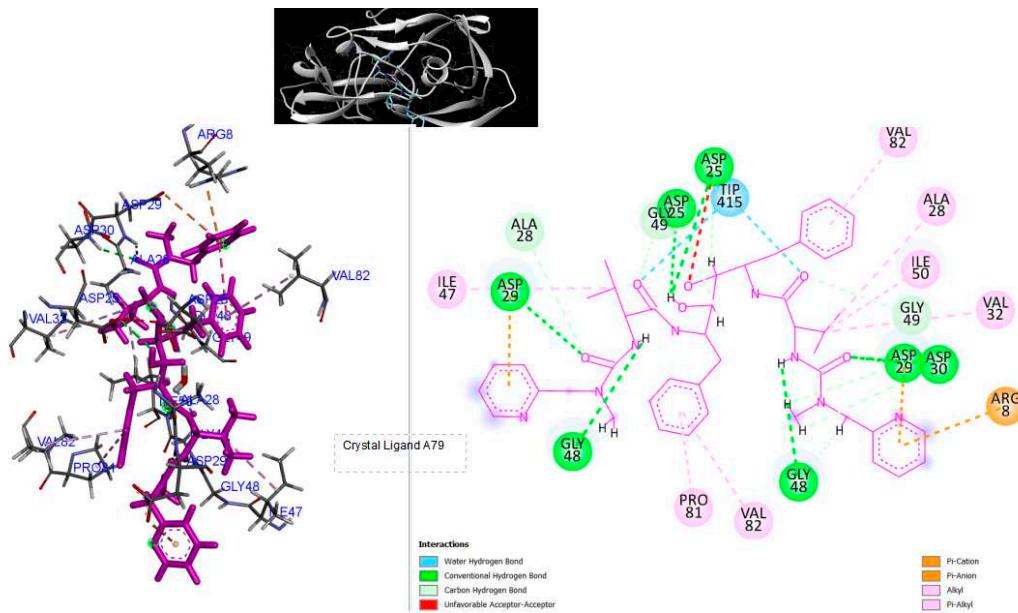
-the most favorable clusters can be visualized online and downloaded on your computer.

In this work, 3D Crystal structures of HIV-1 protease and HIV-2 protease with their crystal inhibitor 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.

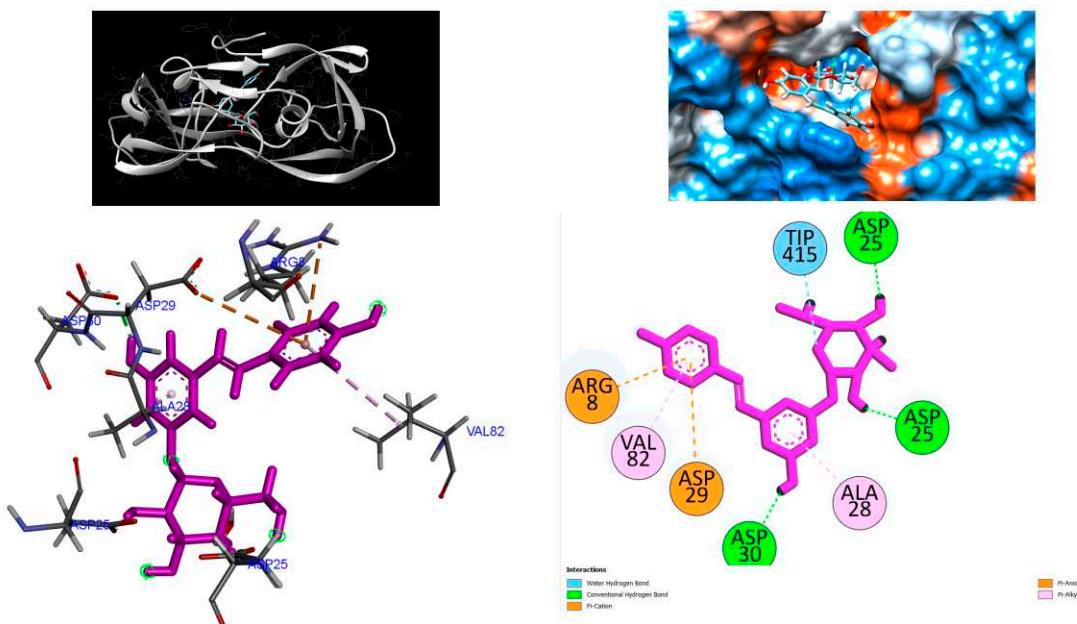
### 3. Results and Discussion

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&ndash;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 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  $\Delta G$  score than the ligand crystal both in the case of HIV-2 protease and HIV-1 : ( Estimated  $\Delta G$  of Polydatin was -9.89 kcal/mol VS Estimated  $\Delta G$  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 active site of HIV-2, while Estimated  $\Delta G$  of Polydatin was -9.47 kcal/mol VS Estimated  $\Delta G$  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 active 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  $\Delta G$  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  $\Delta G$  score of -9.89 kcal/mol of  $\Delta G$  when Polydatin binds with HIV-2 protease ; VS a good  $\Delta G$  score of -9.47 kcal/mol of  $\Delta G$  , when Polydatin binds with HIV-1 protease.

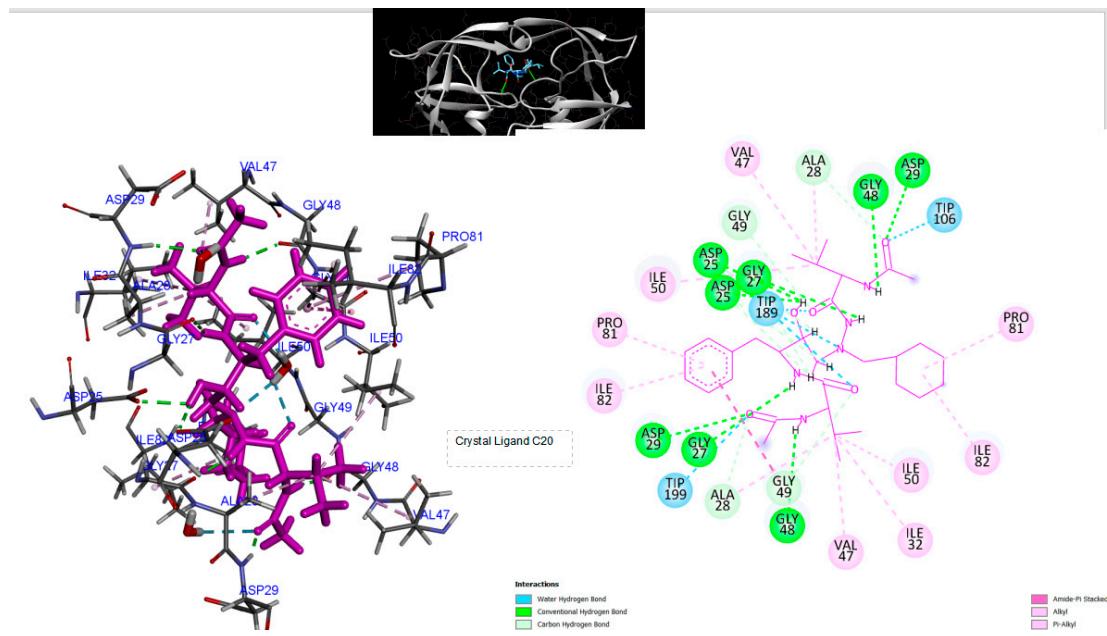
These results are significant not only because they demonstrate the ability of polydatin to bind better with HIV-2 protease compared to when it binds with HIV-1 protease, even though they have a 54% similar sequence between them [15], but also because the polydatin in the active site of these proteases 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 Figs. 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.



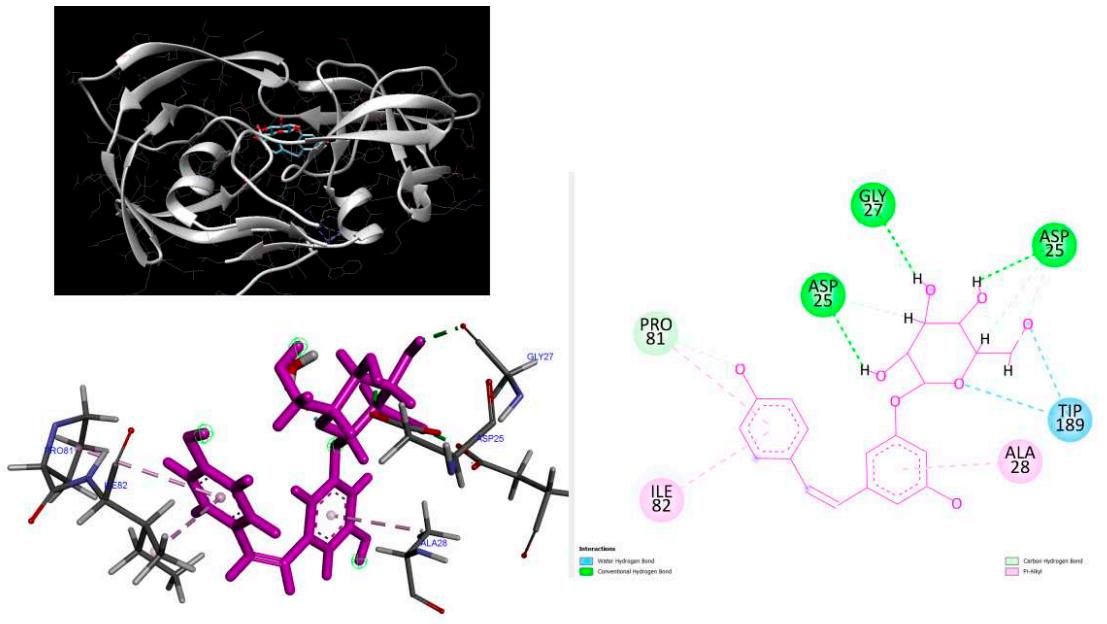
**Figure 3.** 3D Crystal structures of HIV-1 protease and 2D Diagrams residues interactions that occur between HIV-1 protease amino acid residues and atoms in crystal ligand A79: [N-(1-BENZYL-(2S,3S)-2,3-DIHYDROXY-4-[3-METHYL-2-(3-METHYL-3-PYRIDIN-2-YLMETHYL-UREIDO)-BUTYRYLAMINO]-5-PHENYL-PENTYL)-3-METHYL-2-(3-METHYL-3-PYRIDIN-2-YLMETHYL-UREIDO)-BUTYRAMIDE ] 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 Crystal 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	Estimated
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			(kcal/mol)	$\Delta G$ (kcal/mol)
		HIV-2		
1HII	PROTEASE	Polydatin	-780.51	-9.89
		HIV-1		
1HVK	PROTEASE	Polydatin	-770.76	-9.47
		Crystal		
1HII	PROTEASE	Ligand C20	-814.83	-12.14
		Crystal		
1HVK	PROTEASE	Ligand A79	-822.14	-12.54

#### 4. Conclusion

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  $\Delta G$  of polydatin with HIV-2, it was reported at -9.9 kcal/mol versus -9.5 kcal/mol.

These computational results are very promising, although *in vitro* and *in vivo* studies are necessary to confirm our findings.

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**Conflict of Interest:** Authors declare that they do not have any conflict of interest

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