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Research Paper

Computational analysis of polydatin, ergotamine, and dydro-ergotamine with apoptotic protease-activating factor 1 (Apaf 1) by docking-based virtual screening with the PyRx tool

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Abstract— In this short communication, we performed Autodock Vina and Autodock-4, using both hundreds of natural compounds and hundreds of drugs with protein apoptotic protease activating factor 1. The goal of this method was to understand, which of the selected drugs and screened natural substances binds better to this protein and which chemical bonds are involved. The technique used for this aim was the Virtual Screening Tool performed by the Pyrx program. From docking results Calculations performed by Autodock Vina, Polydatin, Ergotamine, and Dydro-Ergotamine showed excellent binding energy scores (-10.1, -10.5, and -12.1 kcal/mol, respectively). All these results lead us to conclude that they could have a Key role in the apoptosis process, even if further studies such as computational and biological tests are necessary.

Keywords— APAF-1,autodocking approach, Autodock Vina and Autodock-4

1. Introduction

Caspases are essential in the cell to carry out apoptosis, which is programmed cell death. They are a group of proteases with cysteine in the active site (short for cysteine-aspartase) [1-5]. There are two types of caspases: the “initiator” caspases (caspase-2, -8, -9, -10) which cleave inactive pre-forms of other caspases called “effector” (caspase-3, -6, -7) activating them; the effector caspases, in turn, will cut specific protein substrates, starting the apoptotic process. The initiation of the apoptotic cascade is regulated by caspase inhibitors; initiator caspases are activated upstream by “adapters” [1-5]. Caspases-1, -4, -5, -11, -12, -13, -14 are involved in the maturation of pro-inflammatory cytokines and are called inflammatory caspases Apoptotic protease activating factor 1 (Apaf-1) controls caspase activation downstream of the mitochondria. [1-5].

We investigate by computational methods protein apoptotic protease activating factor 1 both drugs and natural compounds in order to study their the binding energies, by Autodock Vina Algorithm [7] in the Binding Site pocked of Apaf 1 target [1],[9,10].

2. Related Work

The protein apoptotic protease activating factor 1 (Apaf 1) was identified in the laboratory of Xiaodong Wang as an activator of caspase-3 in the presence of cytochrome C and dATP [1],[9].

3. Calculation

To understand the possible biological role of APAF-1 with drugs and natural compounds we performed computational analysis focused on Molecular docking approach.Indeed, preliminary studies of Virtual Screening with Pyrx program were carried out which, through Autodock [11], assigns a binding energy score value (kcal/mol) thus allowing their comparison. It is well known that when there are very negative binding energy score values, the target molecule theoretically has a greater binding affinity with the target protein. Indeed, he binding energy of the best pose from each compound was studied.

4. Experimental Method

The protein apoptotic protease activating factor 1 (APAF 1) was downloaded from the Protein Data Bank (PDB 1Z6T) [1] and was accurately prepared before performing the Docking

analysis. This crystal protein was complexed with Adenosine-5' Diphosphate (ADP).

To correctly prepare the molecular docking analysis, the ADP ligand was separated from the protein, and the Hydrogens and Gasteiger charges were added by the MGL tool[12]. Virtual Screening analysis and Molecular docking tests are carried out by taking the coordinates X, Y, and Z of crystal ligand ADP to validate the binding energies score accurately.

Coordinate Grix box of APAF-1 by Autodock Vina: center_x = -2.82678022107, center_y = 41.9749771364, center_z = 70.6202957692. Size in Ångström units of X,Y,Z is 25 (Å). Coordinate Grix box of APAF-1 by Autodock-4: center_x = -2.163, center_y = 43.295, center_z = 72.001. Size in Ångström units of X,Y,Z is 40 (Å).

5. Results and Discussion

The focus of this paper was to perform docking calculations based on the study of binding energy scores of drugs and natural compounds with APAF-1(apoptotic protease activating factor-1) [1-5]. The crystal structure of this protein is shown in Fig. 1. This protein was taken by Protein Data Bank, and it was complexed with Crystal ligand Adenosine-5' Diphosphate (ADP). After performing the Virtual Screening investigation with the Pyrx program, [11] in the Binding Site pocked of this protein, comparing hundreds of drugs and hundreds of natural molecules, only the polyphenol called Polydatin and the drugs Ergotamine and Dydro-ergotamine showed excellent Binding energy values in Kcal /mol units.

Table 1 shows the results of docking calculations. Next. results of Docking calculations of Polydatin, Ergotamine, and Dydroergotamine respectively, are characterized by the Discovery Studio Visualizer program and they are shown in Fig.2, Fig.3, and Fig.4 respectively. In this figure, we reported all binding bonds, both hydrophobic and H-bonds involved in Polydatin, Ergotamine, and Dydroergotamine with protein apoptotic protease activating factor-1). Once you have discovered which are the compounds that bind best on the active site of the APAF-1 protein, through Autodock Vina, we performed the following analysis of Autodock 4, with MGL -Tool, by obtaining optimal binding energy values with values similar to those obtained with Autodock Vina, except for Polydatin which showed a lower binding capacity than Ergotamine and Didro-Ergotamine respectively.

The results of docking calculations performed by Autodock-4 are shown in Table 2.

In Fig. 5-7, we have reported all binding involved, both hydrophobic and H-bonds with docked Polydatin, docked Ergotamine, and docked Dydroergotamine together protein apoptotic protease activating factor-1). These investigations were evaluated by automatic LIGPLOT analysis.

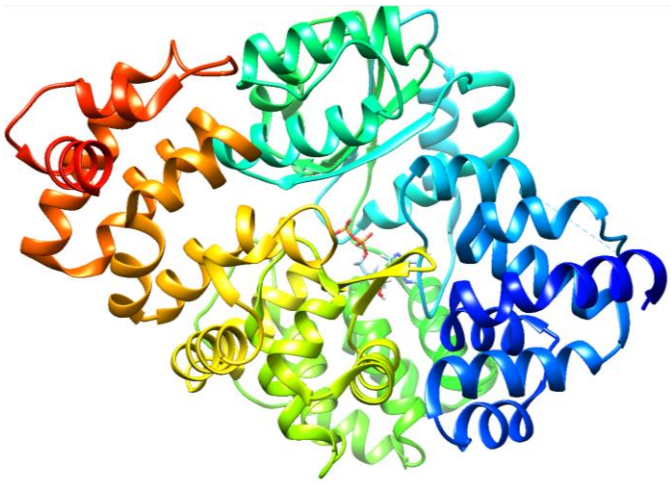

Figure 1. protein apoptotic protease activating factor 1 in complex with ADP. This figure was reproduced by Chimera program

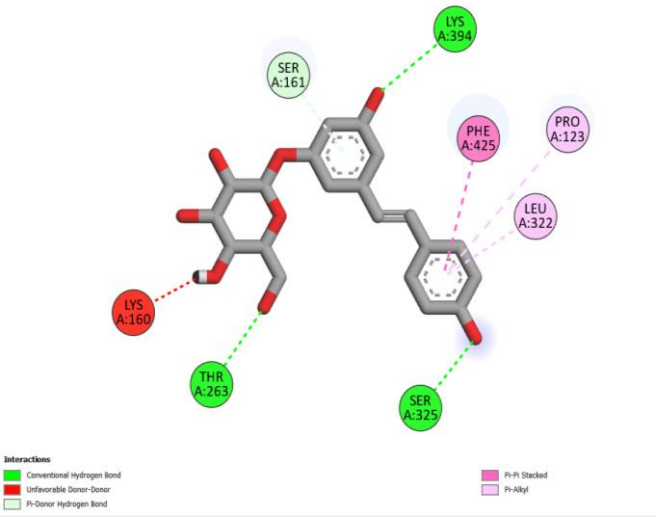

Figure 2. 2D ligand-protein interaction diagrams of Polydatin with APAF-1 in Ligand Binding Site pocked. The figure was reproduced by Discovery Studio.

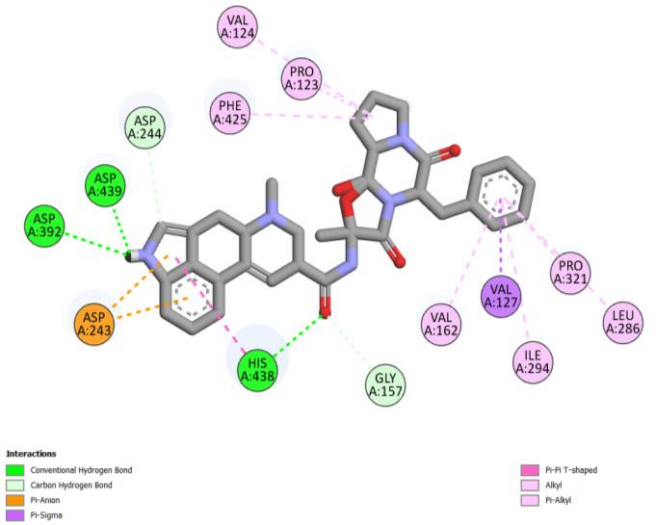

Figure 3. 2D ligand-protein interaction diagrams of Ergotamine with APAF-1 in Ligand Binding Site pocked. The figure was reproduced by Discovery Studio Visualizer.

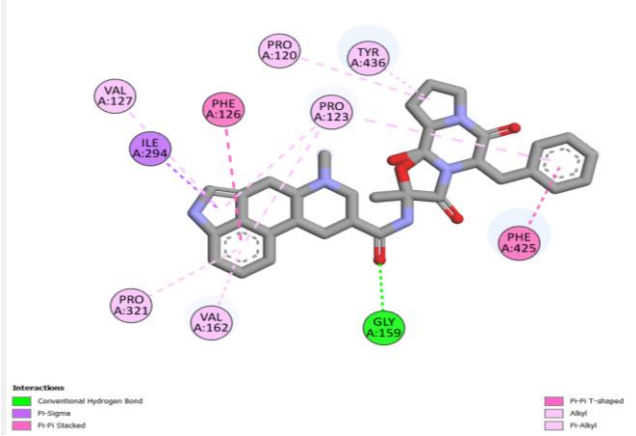

Figure 4. 2D ligand-protein interaction diagrams of Dydro-ergotamine with APAF-1 in Ligand Binding Site pocked. The figure was reproduced by Discovery Studio Visualizer.

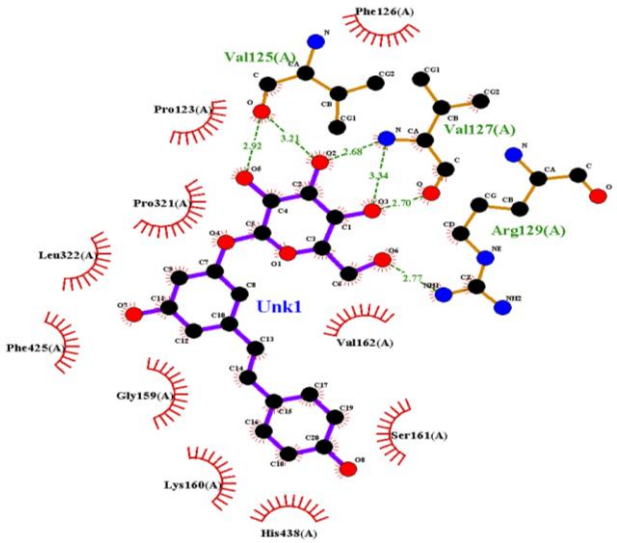

Figure 5. 2D ligand-protein interaction diagrams of Polydatin with APAF-1 in Ligand Binding Site pocked. The figure was reproduced by LIGPLOT tool.

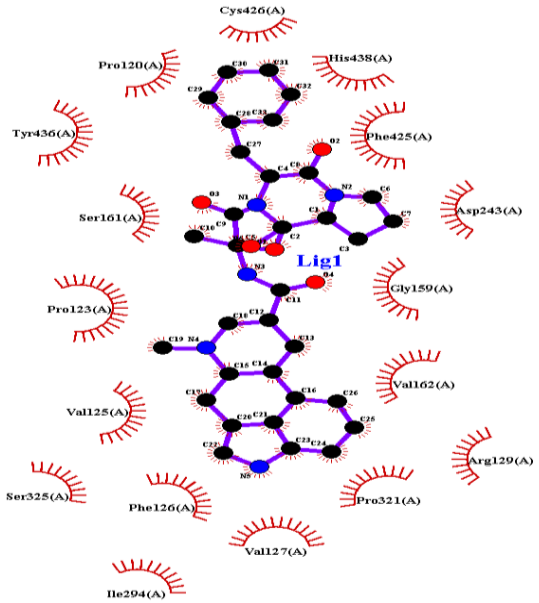

Figure 6. 2D ligand-protein interaction diagrams of Dydro-ergotamine with APAF-1 in Ligand Binding Site pocked. The figure was reproduced by LIGPLOT tool.

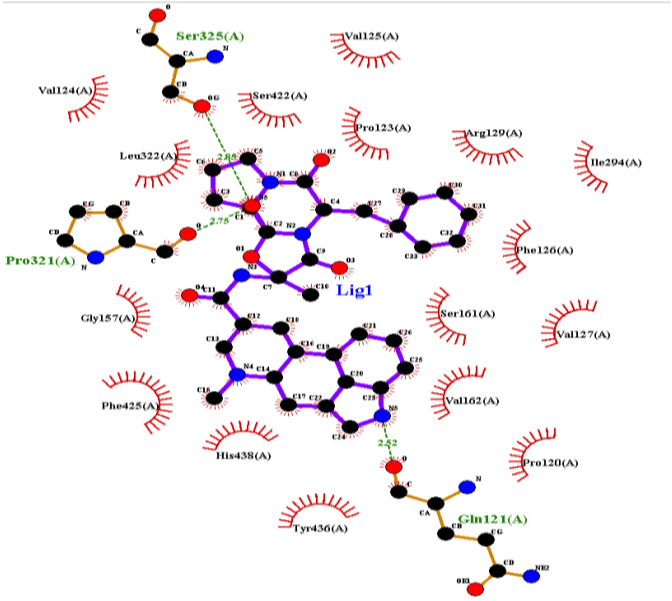

Figure 7. 2D ligand-protein interaction diagrams of Ergotamine with APAF-1 in Ligand Binding Site pocked. The figure was reproduced by LIGPLOT tool.

Table 1. Comparison best poses of binding energies of three best compounds in Binding Site pocked of APAF-1 performed by Autodock Vina

Compounds	Binding Energies (kcal mol^{-1})
Polydatin	-10.1
Ergotamine	-12.5
Dydroergotamine	-12.1

Table 2. Comparison best poses of binding energies of three best compounds in Binding Site pocked of APAF-1 performed by Autodock-4

Compounds	Binding Energies (kcal mol^{-1})
Polydatin	-8.39
Ergotamine	-10.78
Dydroergotamine	-12.50
Crystal Ligand ADP	-10.94

6. Conclusion and Future Scope

In this short communication, we performed Autodock Vina and Autodock-4 Algorithms for natural compounds and drugs with protein apoptotic protease activating factor 1 to which of the drugs and natural substances binds better to this protein and which chemical bonds are involved. The first analysis, by Autodock Vina Polydatin, Ergotamine, and Dydro-Ergotamine are potential compounds to be bound in the Acitive site of APFA-1. With the second method that is more accurate in terms of binding energies, only Dydro-ergotamine showed excellent binding energy scores of about -12.5 kcal/molt, with respect to crystal ligand ADP of about -10.9 kcal/mol.

This means that Dihydro-ergotamine, used in the acute treatment of migraine, could be involved in the apoptosis process. It should be underlined that the natural molecule called Polydatin showed excellent results only with Autodock Vina, partially demonstrating that it could also play an important role with APFA-1. To confirm our findings, further computational and biological studies (in vitro and in vivo) are needed.

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

Authors' Contributions
Ivan Vito Ferrari researched literature, involved in protocol development and conceived the study. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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