International Journal of Scientific Research in Computer Science and Engineering
Vol.10, Issue.3, pp.26-30, June (2022)

Research Paper

E-ISSN: 2320-7639

Molecular Docking Reveals the Pharmacological Properties of Natural Molecules as Potential Candidates in Similar Behaviors of Aliskiren

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Available online at: www.isroset.org

Received: 26/Apr/2022, Accepted: 28/May/2022, Online: 30/Jun/2022

***Abstract*—**Hypertension account for one of the most causes of cardiovascular diseases (CVDs) progression leading to disability and mortality worldwide and there are several antihypertensive drugs to manage this condition. In spite of the presence of several drugs, the research in this sector keep going forward because the final target is the personalized medicine with totally or very low side effects. In this paper we want to study a new class like last frontier of antihypertensive drugs. The progenitor is aliskiren one drug recently approved like direct inhibitor of renin and consequently the next cascade of angiotensin, aldosterone that control the blood pressure. In this paper we want to evaluate a series of new natural molecules in order to find the best molecules that act similarly the aliskiren and possibly with more antihypertensive efficacy and without side effects. For the goal, several natural compound has been screened measuring the capacity of singles molecule of binding in the site of the renin. We did a comparison with the aliskiren. As for the methodology we used a computational approaches with appropriate software to measure the docking step measuring parameters like binding energy on the site of interaction with the molecules evaluating potential inhibitors of renin. The protein Crystal Structure of Renin and 44 natural compounds were downloaded from Protein Data Bank and accurately prepared before to run with Autodock Vina and Autodock 4 analysis. **Results:** Two potential candidates were found to have a superior binding with renin, compared to Aliskiren, with a range of 2-3 kcal/mol Binding energy scores. In favour of this simple bioinformatics investigation, we evaluated, previously a validation method of docking analysis to support this hypothesis. **Conclusions:** this study offer a stimulus for further research in this last groups of antihypertensive drugs, that block the RAAS pathway at the point of activation and recognized as the preferred pharmacologic approach system.

***Keywords*—** Renin inhibitor; Aliskiren , AutoDock Vina Tool

I. INTRODUCTION

In spite of a huge numbers of antihypertensive drugs classified in five principal classes the research in this sector keep going forward because the final target is to reduce at minimal the concomitant side effects related to antihypertensive drugs [1,2]. Recently it is introduced like last frontier of progenitor and approved like new drug Aliskiren Rasilez® as direct inhibitor the renin, as consequence all the cascade determined from renin fail to result in a decreasing blood pressure value. We report a detail structure of Crystal Structure of Renin with inhibitor Aliskiren (Fig.1) 3D plot and 2D plot residues (Fig.2).

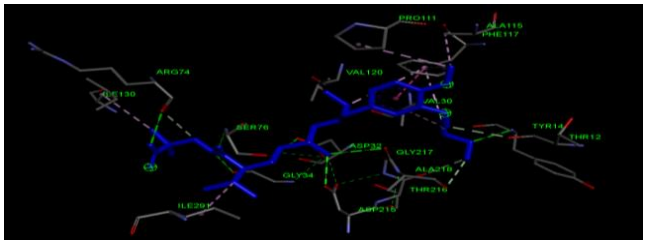


Figure 1. Structural PDB2V0Z 3D plot residues interactions of Crystal of Renin with inhibitor10 (Aliskiren) evaluated by Discovery Studio Biovia program.

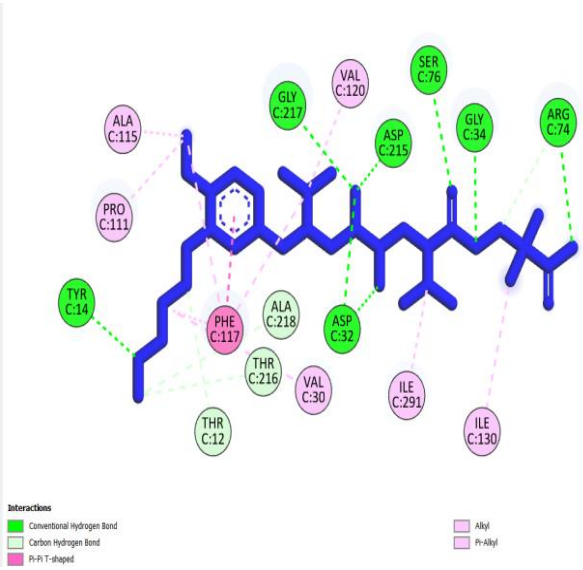


Figure 2. Schematic representation PDB2V0Z of 2D plot residues interactions of Crystal Structure of Renin with inhibitor 10 (Aliskiren) evaluated by Discovery Studion Biovia program.

Table 1. Comparison Binding affinity (kcal/mol) of ID PDB Code: 2V0Z Aliskiren and a series of natural compound with a single receptor-binding domain The Docking was done by Autodock Vina with Pyrx program.

Ligand	Binding Energy Kcal/mol	Ligand	Binding Energy Kcal/mol
Aliskiren	-9.5	Isorhamnetin	-7.8
(-)-Epicatechin	-7.3	Kaempferol	-7.9
2-Azahypoxanthine	-5.8	Lutein	-7.9
Apigenin	-7.7	Luteolin	-7.8
Ascorbic_acid	-5.2	Malvidin	-7.3
Caffeine	-5.8	Myricetin	-7.7
Camptothecin	-8.7	Naringenin	-7.8
Cetocycline	-9.3	Naringin	-9.1
Cianidanol	-7.9	Pelargonidin	-7.7
Coprinol	-7.0	Peonidin	-7.8
Curcumin	-7.6	Petunidin	-7.6
Cyanidin	-7.7	Polydatin	-8.4
Daidzein	-7.8	Pterostilbene	-6.9
Delphinidin	-7.6	Quercetin	-7.8
Epigallocatechin	-7.3	resveratrol	-7.0
Eriodictyol	-7.8	Rutin	-9.6
Genistein	-8.0	Silymarin	-8.6
Ginkgetin	-10.0	Sinefungin	-7.6
Glycitein	-7.7	Tangeretin	-7.2
Hesperetin	-7.8	Theaflavin	-9.4
Hypericin	-9.3	Zeaxanthin	-7.3
Isatin	-6.3	theophylline	-5.5
		Theobromine	-5.5

Today, computational chemistry [3] and chemoinformatics play a key role in early phase drug research, both as drug repositioning or drug package leaflet and identifying the most promising candidates for experimental investigations. Two major strategies have been employed for virtual screening: pharmacophore modeling and molecular docking.. Ligand docking is a widely used approach in virtual screening.[4,5]In this paper we perform an in-silico evaluation of 44 (Table 1 list of molecules), natural most alkaloids by molecular docking approach, estimated by AutoDock Vina with PyRx Virtual Screening Tool. The main of this silico analysis was calculated in the receptor-binding domain (RBD), renin receptors. Our strategy of this short study was first, to evaluate "blind docking method" all the entire protein, calculating the affinity (kcal/mol) of several natural substances, identifying the highest ones. The second step was to compare the affinities between Aliskiren and natural substances. One of the largest and most diverse groups of alkaloids are Rutin and Gingketin compounds recently study to fight covid-19 [6,7] and others of these have been isolated from a number of Menispermaceous plant species used traditionally for malaria treatment. In Fig.3 is reported the molecular interaction of renin and Aliskiren.

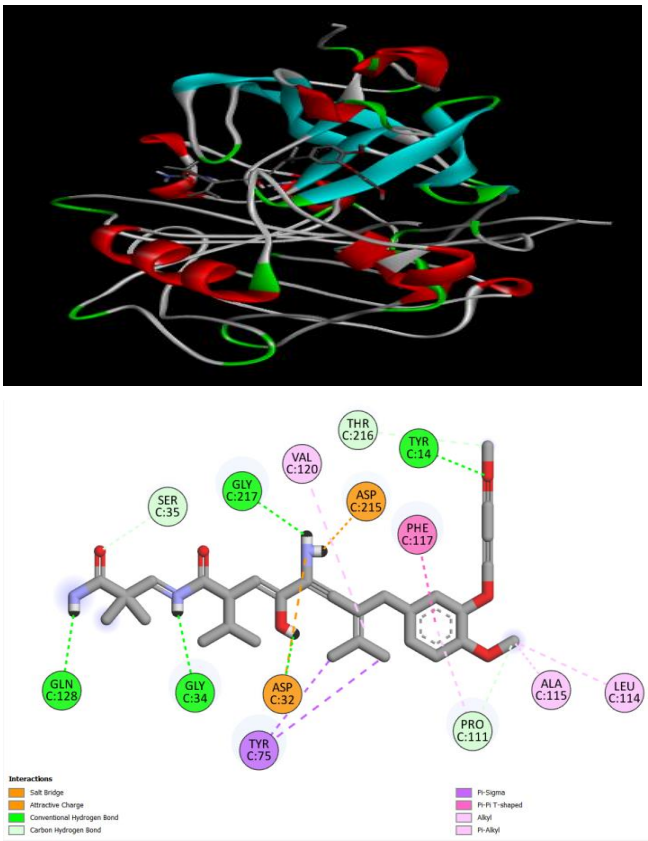


Figure 3. Comparison of best predicted binding energy (Kcal/mol) in ligand Binding site pocket 3a and 3D plot residues interactions of Crystal Structure of Renin with docked Aliskiren -9.5 kcal/mol 3B 2D plot residues interactions of Crystal Structure of Renin with docked Aliskiren -9.5 kcal/mol.

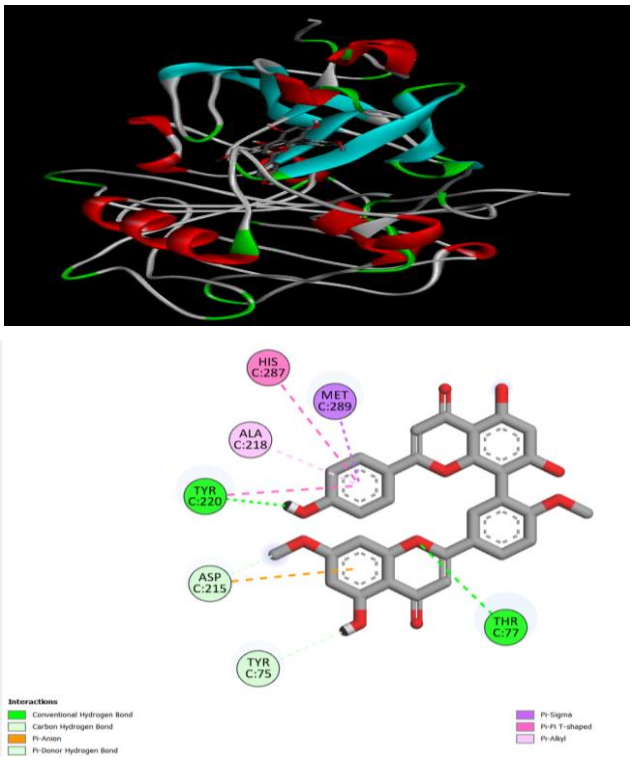


Figure 4. Comparison of best predicted binding energy (Kcal/mol) in ligand Binding site pocket 4a 3D plot residues interactions of Crystal Structure of Renin with docked Ginkgetin -10.0 kcal/mol 4B 2D plot residues interactions of Crystal Structure of Renin with docked Gingketin -10.0 kcal/mol.

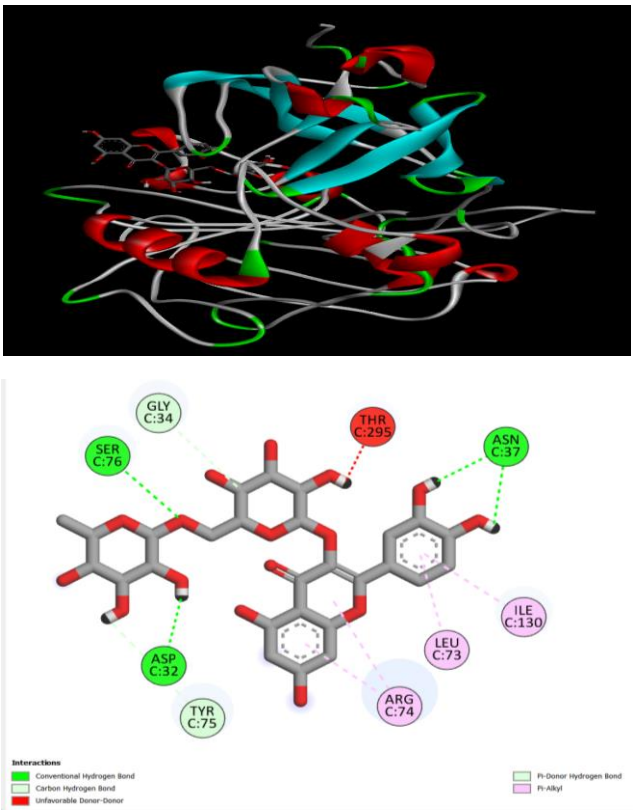


Fig.5 Comparison of best predicted binding energy (Kcal/mol) in ligandBinding site pocket 5a 3D plot residues interactions of Crystal Structureof Renin with docked RUTIN -9.6 kcal/mol 5B 2D plot residues interactions of Crystal Structure of Renin with docked Rutin -9.6 kcal/mol. Structural analysis of reproduced by Pymol software

From our Virtual Screening calculated by Pyrx program, only two best docked natural compounds that (Gingetin and Rutin) worth to perform by Autodock 4 function score in Ligand Binding Site of Crystal Structure of Renin (Fig.4 e Fig.5).

II. Related Work

The paper is a bioinformatician approach to evaluate in silico the potential candidates against renin, evaluating a series of natural compound as screening, measuring the binding energy linked to force of binding in the receptor pocket where acts renin as competitive antagonist. In this paper we perform an easy and rapid screening through the analysis of Binding Affinity, estimated by Autodock Vina with PyRx software of natural compound listed.

III. Methodology

We reported the protein Crystal Structure of Renin (Fig.1) were downloaded from Protein Data bank https://www.rcsb.org (PDB 2V0Z) and they are accurately prepared, saved in PDB format. The first step, was the removal of ligands and crystallized water molecules from crystal protein, using Chimera software (https://www.cgl.ucsf.edu/chimera/) Later, Polar Hydrogens and Kollmann charges were added with MGL-Tool, or called AutoDockTools (https://ccsb.scripps.edu/mgltools/downloads/) and converted to PDBQT format. Regarding best compounds preparation, (44 natural compounds were manually downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in 3D Conformer SDF and they are minimized by Avogandro program with FFFF94 force field with Optimization Algorithm Decrescent and all Hydrogens and Gasteiger charges were added by Autodock Tools and finally they are converted in pdbqt format, before to run Autodock 4 docking analysis.

-Protein Preparation renin

The Workflow protein preparation steps: a) Delete co-crystalized ligand and water in the protein by Chimera Software b) Add Kollmann charges and add only Polar Hydrogen in the protein, by MGLTools 1.5.6/(known AutoDock Vina 4) c) Verify, repair missing residues crystal renin to perform protein structure, by Molegro Virtual Docker Software d) Energy minimization step by Swiss PDB Viewer. e) Final molecules has been converted into pdbqt format ready to docking process by Pyrx Software and AMDock Software.

-Ligand Preparation

All the compounds were optimized prior to docking using AutoDock Vina. Polar hydrogens were added and Gasteiger charges were computed of each compound in the library. Later, the compounds were saved in pdbqt format for docking purpose. Molecular docking of the natural substances alkaloids was conducted by AutoDock Vina. Total 9 Confirmations were generated for every compounds. After docking top 44 compounds [based on docking scores (kcal/mol)] were chosen and visually inspected using Discovery Studio Biovia (Fig,3,4,5).

Workflow Ligand preparation steps: The same steps preparation (b,c,d) were evaluated for the natural substances alkaloids. 3D Conformers were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/).

-Pyrx Virtual Screening Tool

PyRx is a Virtual Screening software for Computational Drug Discovery that can be used to screen libraries of compounds against potential drug targets. In this paper we perform Molecular docking analysis, in order to estimate the Affinity (kcal/mol). Binding affinity (Kcal/mol) of ID PDB: renin, Aliskiren, natural substances, was calculated by AutoDock Vina with Pyrx and Chimera Software[3].

Grid Box parameters for Autodock

4 docking npts 44 40 40, num.grid points in xyz spacing 0.375 Grid center 7.163 ; 46.084; 69.01 : xyz-coordinates smooth 0.5 store minimum energy w/in rad(A) Population Size: 250000

Parameters of crystal Structure of Renin Grid Box parameters for Docking receptor

exhaustiveness = 8. center_x = 6.70615868137 center_y = 44.7373136908 center_z = 67.9684947593. size_x = 25.0 size_y = 25.0 size_z = 25.0.

IV. Results and Discussion

In (Table 1) is reported the best molecules found in the docking analysis with the binding energy The result found two best molecules rutin and gingketin with the values of binding affinity of -7,18 kcal/mol, and -8.51 kcal/mol respectively. The value of docking of Aliskiren is -7.87 kcal/mol. It is worth to mention that rutin and gingketin showed a versatile pharmacological activities as reported [7]. Besides Rutin and Gngketin are reported to have several antibiotics and antiviral effects and the assumption of mechanism could be related to inhibit important enzymes crucial for the microrganisms and some proteases like SARS-COV-2 main proteases and thus preventing replication of the virus [8,11,12,13]. Besides there is also a sort of correlation with rutin to have similar potential effect as inhibitor renin in previous study. There are still controversial discussion in the interaction with ACE2 enzymes that contribute to have some effect in the covid prevention. ACE inhibitors are notoriously drugs inhibitors of the ACE block the formation of Ang II but also cause a respective increase in the concentrations of Ang I that can subsequently be converted to Ang II by other pathways, such as the chynase system. Also, ACE inhibitors are not specific for RAAS, preventing inactivation of bradykinin and substance P that are known to mediate some of the side-effects of ACE inhibitions such as cough and angioedema.

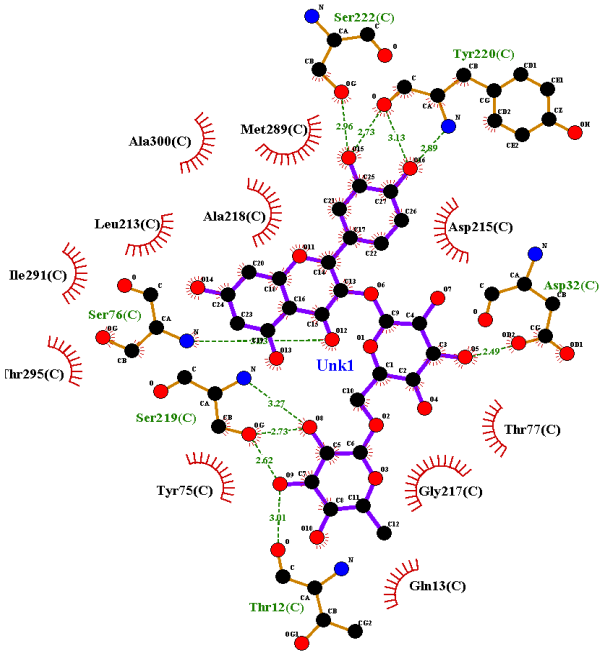
For this reason the new class of drugs leading by aliskiren could be more interesting in reducing the side effects thanks to act in a different site of RAAS system.[10,14,15] One problem about aliskiren is the accumulation following multiple once-daily administration as indicated by the accumulation ratios of between 1.4 and 3.9, with the accumulation being more pronounced at higher doses [9].

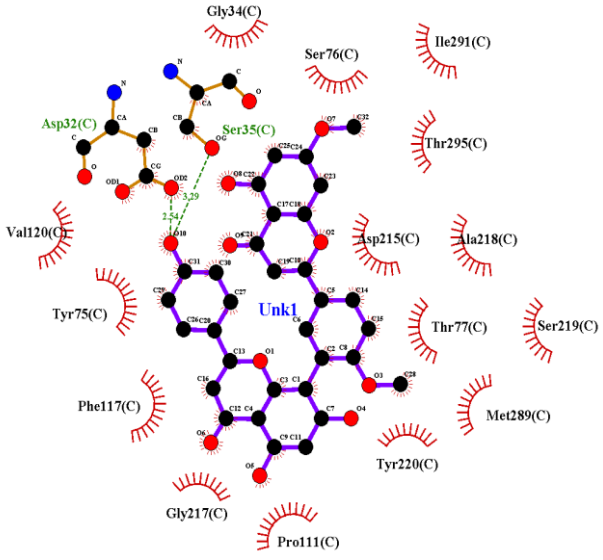
So new molecules with similar behaviours with aliskiren could show less side effects. It is know that the first renin inhibitors were synthesized already more than 30-years ago [10] so actually it is a long time that there is interest in drugs of direct inhibition of renin. An other aspect of aliskiren is, despite an high potency for human renin the drug show a relatively low oral bioavailability of the drug so remain a margin of tolerability and efficacy with new molecules. What's more aliskiren look like to be a potential candidate in the context of SARS-CoV-2 infection that requires further investigation [19] and so our investigation could be useful to bring to mind new hints to fight covid infection. For example the molecular docking methodology is used to demonstrate the cooperation between a small molecule and a protein at the nanoscale, useful to ease the description the behavior of small particles in the binding sites of the proteins and explain key biochemical processes and many computational tools have been developed and are widely used which empower us to find information structure-activity relationships.

One big limitation of developing new antihypertensive drugs is linked to the strong competition with several drugs classified in others groups. Remain a big challenge to manage from the physician several antihypertensive drugs with a more close personalized medicine.

Table. 2 Docking by Autodock 4 function score (kcal/mol) by MGL Tool program

Compounds	*Estimation Binding Energy score (kcal/mol)*	*Estimatation of inhibition constant Ki*
Aliskiren	-7.87	1.71 µM
Rutin	-7.18	5.5 µM
Gingetin	-8.51	570.84 nM





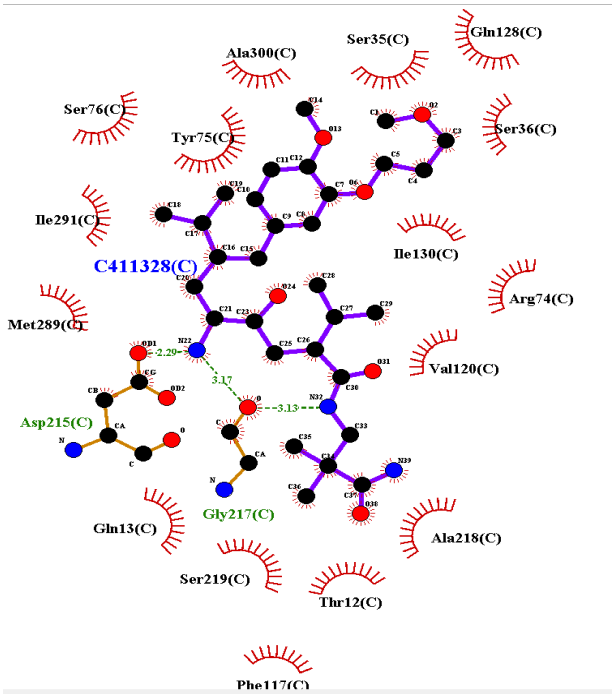


Figure 6. Structure of 2D residues interacton of crystal Structure of a-Renin with docked a) Aliskiren, b) rutin, c) gingketin respectivley by Ligplot program.

Further investigations is necessary choosing some better alkaloids, and blind docking and docking in the pocket RBD region, always comparing it to the Aliskiren.

V. CONCLUSION and Future Scope

The final result shown that two molecules Rutin and Gingketin represent the good potential candidates to further investigation and stimulate the extraction and built a lead molecule to obtain in the further steps potential drugs with scarce of null side-effects without missing efficacy of antihypertension.

Declaration of Competing Interest

The authors declare they have no potential conflicts of interest to disclose.

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