ORIGINAL ARTICLE

Investigation renin inhibitor activity from flavonoids derivates by *in silico* study

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ABSTRACT

Flavonoids have various pharmacological activities, such as antihypertensive, anticancer, and and antidiabetic effects. Several studies have shown that luteolin, quercetin, kaempferol, myricetin, naringenin, hesperetin, and epicatechin have antihypertensive effects, but the mechanism of action has yet to be discovered with certainty. This study aims to identify flavonoids from luteolin, quercetin, kaempferol, myricetin, naringenin, hesperetin, and epicatechin as renin inhibitors through *in silico* study; seven flavonoid compounds were docked with 2V0Z with renin inhibitor (Aliskiren) in humans (Homo sapiens 6 LU7) using AutoDock v4.2.6. SwissADME was used to evaluate the pharmacokinetic characteristics of these substances. Results molecular binding of luteolin, quercetin, kaempferol, myricetin, naringenin, hesperetin, and epicatechin, has potential as renin inhibitors with affinity energy values lower than those of aliskiren of −9.3; −9.3; −10.0; −9.2; −9.9; −9.3; and −9.7 kcal/mol. The interactions of these seven compounds have the same catalytic activity as aliskiren on two aspartic acid residues, Asp32 and Asp215. The analysis of pharmacokinetic profiles and the search for physical and chemical properties showed that the seven compounds violated three of the five Lipinski rules, while aliskiren violated one. Hesperitin, kaempferol, and naringenin had similarities with aliskiren on the amino-acid residues in the renin-binding pocket. However, based on pharmacokinetic analysis, the three compounds had an oral pharmacokinetic profile that could have been better than aliskiren.

Key words: Aliskiren, flavonoid, *in silico*, renin inhibitor

INTRODUCTION

A myocardial infarction, a stroke, heart failure, and renal disease are all forms of cardiovascular disease, and hypertension is a risk factor for all these conditions. The pathophysiology of hypertension can be attributed to many different factors, including, but not limited to, an increase in the activity of the renin–angiotensin–aldosterone system (RAAS), the kinin–kallikrein system, and the sympathetic nervous system.[1] Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor antagonists (ARA2) are two antihypertensive medications that inhibit the RAAS. Both of these medications have some undesirable side effects, although they are effective at lowering hypertension and protecting organs. Inhibition of negative feedback by ACEi and ARB can cause a rise in plasma renin activity, which can leading to increased damage to the target organs, such as renal failure and left ventricular hypertrophy.[2]

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Renin inhibitors can be developed as drugs because they have good bioavailability. Renin is an enzyme identified as an attractive target for developing antihypertensive medicines. Renin inhibitors have common side effects because they have the potential to prevent the hormonal complex system from occurring at the beginning of its activation.[3] Aliskiren is an antihypertensive medication that belongs to a newly discovered class of renin inhibitors. Aliskiren treatment on its own is comparable to that of ACEi and ARB. Aliskiren has side effects of angioedema, diarrhea, headache, nasopharyngitis, fatigue, upper respiratory tract infections, and back pain.[4] It is still necessary to find other renin inhibitors from natural materials. One of the steps to find compounds that are efficacious as drugs before *in vitro* and *in vivo* studies is *in silico* studies.[5]

Flavonoids represent the main class of polyphenols. In addition to having antioxidant effects, flavonoids exhibit various pharmacological activities such as antihypertensive, anticancer, and antidiabetic effects.[6] Flavonoids have several derivatives, such as flavonols, flavones, flavanones, catechins, anthocyanidins, isoflavones, dihydroflavonols, and chalcones. Several studies have shown that flavonols' derivatives such as luteolin, quercetin, kaempferol, myricetin, naringenin, hesperetin, and epicatechin have antihypertensive effects,[7] but the mechanism of action is understood. As a result, *in silico* study is required to ascertain these drugs' mode of action as renin inhibitors.

In silico is one of the methods used to find compounds that can be used as drug candidates. The *in silico* method has many advantages, namely, reducing the number of experimental animals used and needed during experiments and determining the mechanism of drug candidate compounds against their targets in the form of visualization. *In silico* test is used to determine the activity of molecules with selected target cells using molecular docking.[5]

This study aims to discover renin inhibitor compounds from luteolin, quercetin, kaempferol, myricetin, naringenin, hesperetin, and epicatechin through an *in-in silico* study and determine their pharmacokinetic profile through SwissADME application.

MATERIALS AND METHODS

Materials

Aliskiren structure and the human renin protein structure were retrieved from the Protein Data Bank's complex file with PDB ID: 2V0Z; ligands from flavonoid derivatives, namely, luteolin with CID: 46878427, quercetin with CID: 6325870, kaempferol with CID: 6325460, myricetin with CID: 138911139, naringenin with CID: 42607921, hesperetin with CID: 3594, and epicatechin with CID: 14841178 downloaded from PubChem. The ChemOffice Pro v15.00 PerkinElmer, AutoDock v4.2.6 and AutoDockTools, Python Molecular Viewer (PMV 1.5.6), Open Babel graphical user interface, and Discovery Studio Visualizer were used to carry out the *in silico* molecular docking study.

Methods

Macromolecular structure preparation

The macromolecule used was the human renin protein receptor (PDB ID: 2V0Z), obtained from PDB on the https://www.rcsb.org/site. The protein macromolecules were separated from solvents, native ligands, and other unnecessary molecules using AutoDockTools. After the process of cleaning the molecules that are not needed, then a hydrogen atom is added. The preparation results are saved in PDB file format (.pdbqt).

Ligand structure preparation

The ligands used in this study were luteolin, quercetin, kaempferol, myricetin, naringenin, hesperetin, and epicatechin. Ligands are downloaded through the site https://pubchem.ncbi.nlm.nih.gov/in the form of a two-dimensional molecular structure and then saved in SDF file format (.sdf). Furthermore, it was minimized to a three-dimensional molecular structure using the MarvinSketch application, and the preparation results were saved in MOL2 file format (.mol2). Then, the ligand is converted into a PDB file format (.pdbqt) using the AutoDockTools application.

Determination of grid box parameter and redocking

Grid box parameters are chosen by determining the grid box coordinates and size using AutoDockTools. The validation of the docking method is done by reducing protein molecules with native ligands using the AutoDock Vina application.

Docking simulations in computer models (in silico)

Seven different flavonoid compounds were *in silico* molecularly docked as potential renin inhibitors using AutoDock version 4.2.6. (The Scripps Research Institute). To carry out a docking simulation, Lamarckian parameters were used. Accelrys Discovery Studio Visualizer 4.0 was used to visualize the grid box size and placement after they had been validated to research the seven known flavonoid compounds.

Pharmacokinetic properties analysis

Seven flavonoid compounds and their natural ligands' pharmacokinetic characteristics were expected using SwissADME (http://swissadme.ch/).

RESULTS

Figure 1a displays the outcomes of creating the renin protein macromolecule employed in the molecular docking procedure for comparative ligands and test chemicals. In Figure 1b, the findings of the comparison ligand preparation

employed during the technique validation step are shown. Figure 2 depicts the outcomes of the test ligand's production using the protein renin.

Grid box parameter is 35 × 35 × 35 with coordinates center_x = 7246, center_y = 46072, center_z = 69.017, and spacing (angstrom) =1Å. The grid parameter produces the most negative affinity energy value, which is -9.0 kcal/mol and the RMSD value is 1.675Å. The stronger the connection produced, the more negative the affinity energy value, and with the RMSD value of two, the molecular docking approach is valid. Table 1 compares the interactions between the test ligand and the reference ligand (aliskiren) regarding amino-acid residues.

A comparison of amino-acid residues on the test ligand binding with the comparison ligand (aliskiren) is presented in Table 2.

The residues of amino acids in the renin-binding pocket are revealed by the interaction of renin protein receptors with test ligands and aliskiren through conventional hydrogen, hydrogen, and van der Waals interactions, as illustrated in Tables 2 and 3.

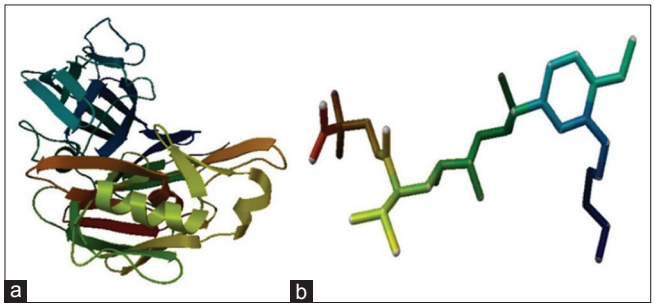


Figure 1: Renin protein macromolecule (a), aliskiren ligand (b)

Figure 3 shows three-dimension visualization of the test ligand and aliskiren using Discovery StudioVisualizer.

DISCUSSION

Flavonoids' fundamental structure consists of two aromatic groups connected by a carbon bridge (C6-C3-C6). The basic structure of flavonoids consists of two aromatic groups joined by a carbon bridge (C6-C3-C6). It has been suggested that flavonoids positively benefit cardiovascular disease, particularly hypertension. However, less information about the therapy of high blood pressure by isolated individual flavonoids is available.[8]

The molecular docking results of seven ligands derived from flavonoid compounds obtained affinity energy values from −9.2 kcal/mol to −10.0 kcal/mol. The energy affinity for the comparison ligand (aliskiren) is −9.0 kcal/mol. The lowest affinity energy value was kaempferol compound which was −10.0 kcal/mol, naringenin was −9.9 kcal/mol, and hesperitin was −9.3 kcal/mol. Based on the affinity energy value, the seven flavonoid-derived compounds have potential renin inhibitors.

Human blood pressure is principally regulated by the renin-angiotensin system, comprised renin, angiotensinogen (AGT), ACE, and angiotensin receptors. AGT between Leu10 and Val11 is broken down by the highly specialized aspartic protease renin, liberating the N-terminal angiotensin I peptide. Angiotensin II, the main physiologically active hormone, is created by ACE's subsequent processing of this peptide. It works by binding to its receptors. The renin-angiotensin system's rate-limiting phase is the breakage of AGT by renin.[9]

Molecular docking results of aliskiren, hesperitin, kaempferol, and naringenin on renin protein macromolecules indicate

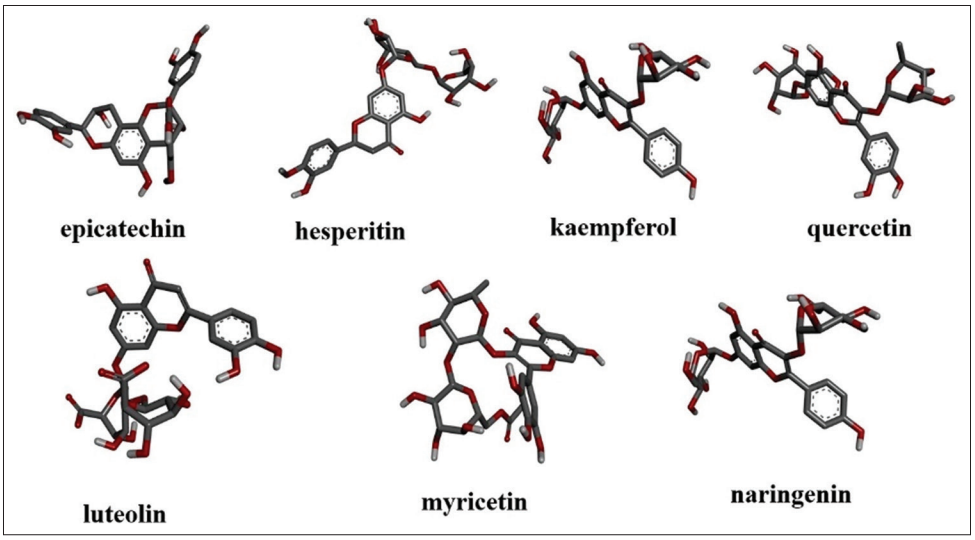
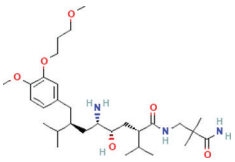
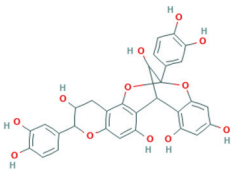
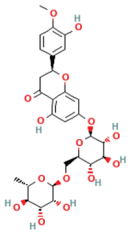
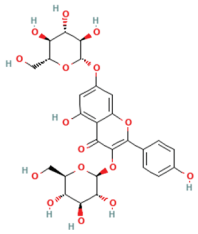
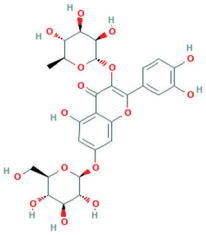


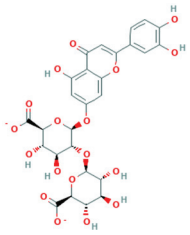
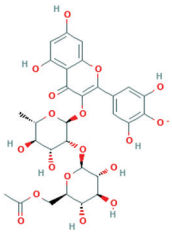
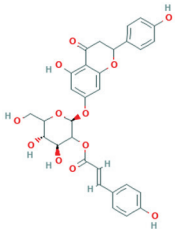
Figure 2: The preparation of the test ligand with protein renin

Table 1: The comparison of amino-acid residue interactions between the test ligand and the aliskiren

Compounds/ molecular weight	Energy affinity (kcal/ mol)	Amino-acid residue
Aliskiren/551.8 g/mol 	−9.0	Asp32, Gly34, Ser76, Asp215, Thr216, Ala115, Ala218, Ala303, Arg74, Gln13, Thr12, Gln128, Gly217, Ile130, Ile291, Leu114, Leu213, Phe112, Phe117, Pro111, Ser35, Ser36, Ser219, Thr77, Thr295, Tyr14, Tyr75, Tyr155, Val30, Val120
Epicatechin/576.5 g/mol 	−9.7	Ala218, Gln13, Gly28, Gly217, His287, Leu110, Leu114, Met289, Phe112, Phe117, Phe242, Pro111, Ser219, Thr12, Thr77, Trp39, Tyr: 9, Tyr75, Tyr220, Val30, Val120
Hesperitin/610.6 g/mol 	−9.3	Asp32, Asp215, Ala115, Ala218, Arg74, Gln13, Gly34, Gly217, Ile130, Ile291, Leu73, Leu114, Leu 213, Met289, Phe112, Phe117, Pro111, Ser35, Ser76, Ser219, Thr12, Thr77, Tyr75, Val30, Val120
Kaempferol/610.5 g/mol 	−10	Asp32, Asp215, Ala218, Arg74, Gln13, Gln128, Gly217, Gly34 Ile130, Ile291, Leu213, Met289, Phe112, Phe117, Pro111, Ser35, Ser76, Ser219, Thr12, Thr77, Thr295, Trp39, Tyr75, Tyr220, Val120
Quersetin/610.5 g/mol 	−9.3	Asp32, Asp215, Ala218, Ala288, Gly34, Gly217, His287, Leu110, Leu241, Met289, Phe112, Phe117, Phe242, Pro111, Ser76, Ser219, Thr77, Tyr75, Tyr220, Val30, Val120

Contd...

Table 1: Contd...

Compounds/ molecular weight	Energy affinity (kcal/ mol)	Amino-acid residue
Luteolin/636.5 g/mol 	−9.3	Asp244, Ala115, Ala218, Ala288, Gln13, Gly217, His287, Leu110, Leu114, Lys239, Met289, Phe117, Phe242, Pro111, Ser219, Thr12, Thr77, Tyr9, Tyr220
Myricetin/667.5 g/mol 	−9.2	Ala115, Ala218, Gln13, Gly78, Gly217, His287, Leu110, Leu114, Met289, Phe112, Phe117, Phe242, Pro111, Ser219, Ser222, Thr12, Thr77, Tyr75, Tyr220
Naringenin/580.5 g/mol 	−9.9	Asp32, Asp215, Ala218, Ala300, Arg74, Gln13, Gln128, Gly34, Gly217, Ile291, Leu213, Met289, Phe112, Phe117, Pro111, Ser35, Ser76, Ser219, Thr12, Thr77, Thr295, Trp39, Tyr75, Tyr220, Val120, Val189

the presence of amino-acid residues that play an essential role in renin binding. The renin-binding pocket's amino-acid residues are displayed in Table 3. Hesperitin, kaempferol, and naringenin are similar to aliskiren. Two homologous lobes make up the complicated structure of renin, which folds primarily in the B-sheet conformation.[9] The active site of renin contains two catalytic triads, Asp32/215, Thr33/216, and Gly34/217, just as other aspartic proteases.[10] By forming hydrogen bonds with the renin's active-site residues, aliskiren and renin's complex will be stabilized. At least five hydrogen-binding interactions keep aliskiren in renin's bound structure stable. Aliskiren is bound inside the cavity by the active-site residues Asp32/215 and Gly34. Arg74, Ser76, and Tyr14 all boost interaction.[11] Aliskiren is a renin inhibitor that resembles a peptide and is unusually hydrophilic. It inhibits the enzyme's catalytic activity by occupying all pockets but the S2 (S3 to S2′). Aliskiren's side chain optimizes to the S3sp subpocket, contributing to its effectiveness as a human renin inhibitor.[12] Aliskiren's hydroxyl group forms a hydrogen bond with the oxygen atoms present in the Asp32 site. A hydrogen bond is formed by the amine group, which interacts with the carboxylic

Table 2: Interaction between renin protein receptors with test ligands and aliskiren

Compounds	Conventional hydrogen	Hydrogen	Van der waals
Aliskiren	Gln128, Gly34, Gly217, Ser76	Pro111, Ser219, Thr216	Arg74, Ala218, Ala303, Gln13, Ile130, Leu213, Phe112, Ser35, Thr12, Thr77, Thr295, Tyr14, Tyr155
Epicatechin	Leu114, Thr12	-	Ala218, Gln13, Gly28, Gly217, His287, Leu110, Met289, Phe112, Phe117, Phe242, Ser219, Thr77, Trp39, Tyr9, Tyr75, Tyr220, Val: 30, Val120
Hesperitin	Asp32, Arg74, Gln13, Ser219	-	Ala115, Ala218, Gly34, Gly217, Ile291, Leu73, Leu114, Leu213, Met289, Phe112, Phe117, Pro111, Ser35, Ser76, Thr12, Thr77, Tyr: 75, Val30, Val120
Kaempferol	Arg74, Gln128, Gly217, Met289, Thr77	Gly34, Thr295	Ala218, Gln13, Ile130, Ile291, Leu213, Phe112, Phe117, Pro111, Ser35, Ser76, Thr12, Trp39, Tyr220
quersetin	Ala288, Ser: 76, Thr77	Gly217, Phe242	Asp32, Asp215, Ala218, Gly34, His287, Leu110, Leu241, Met289, Phe112, Phe117, Ser219, Tyr75, Tyr220, Val30, Val120
Luteolin	Ala288, His287, Leu114, Ser219, Thr77	-	Asp244, Ala115, Ala218, Gln13, Gly217, Leu110, Lys239, Met289, Phe117, Phe242, Thr12, Tyr9, Tyr220
Myricetin	Gln13, Gly217, His287, Leu114, Thr77	-	Ala115, Ala218, Gly78, Met289, Phe112, Phe117, Phe242, Ser219, Ser222, Thr12, Tyr75
Naringenin	Asp215, Arg74, Gln128, Ser219, Thr77	Gly34, Gly217	Ala218, Ala300, Gln13, Ile291, Leu213, Met289, Phe112, Phe117, Pro111, Ser35, Ser76, Thr12, Thr295, Trp39, Tyr220, Val120

Table 3: Amino-acid residues in the renin-binding pocket

Pockets	Characteristic	Importance to binding	Compound	Amino-acid residue
S3	Hydrophobic	Very essential for binding	Aliskiren	Phe117, Ala115 Thr12, Gln13, Pro111, Leu114, Ser219
			Hesperitin	Phe117, Ala115 Thr12, Gln13, Pro111, Leu114, Ser219
			Kaempferol	Thr12, Gln13, Pro111, Phe112, Phe117, Ser219
			Naringenin	Thr12, Gln13, Pro111, Phe112, Phe117, Ser219
S2	Large and hydrophobic	Important for binding	Aliskiren	-
			Hesperitin	Met289
			Kaempferol	Met289
			Naringenin	Met289
S1′	Hydrophobic primarily	Essential for tight binding	Aliskiren	Leu213, Asp215, Ile291, Thr295, Ser76, Gly217
			Hesperitin	Gly217, Leu213 Ser76, Asp215, Ile291
			Kaempferol	Ser76, , Asp215, Gly217, Ile291, Thr295
			Naringenin	Leu213, Asp215, Gly217, Ile291, Thr295, Ala300, Leu213, Ser76
S2′	Polar	Essential for tight binding	Aliskiren	Ile130, Gly34, Ser35, Tyr75, Arg74, Gln128
			Hesperitin	Ile130, Gly34, Ser35, Tyr75, Arg74, Gln128
			Kaempferol	Gly34, Tyr75, Ser35, Arg74, Gln128, Ile130
			Naringenin	Gly34, Ser35, Arg74, Tyr75, Gln128

acid group of Gly217 and the oxygen atom of Asp32. The methoxy group is responsible for filling the S3 pocket on the aromatic ring, which also has the potential to form a hydrogen bond with a secondary amine group located on Tyr14. The formation of a hydrogen bond is caused by combining Ser76's secondary amine group with the amide group. Both propyl groups may be found in positions P1 and P1′, occupying the pockets S1 and S1′, respectively. The terminal amide in position P2′ is responsible for anchoring the amide tail in the active site. This amide establishes a hydrogen bond with Arg74 inside the S2′ pocket.[9,13]

Molecular docking results on flavonoid compounds showed that kaempferol, naringenin, and hesperetin have similar interactions with aliskiren on the amino-acid residue of protein renin. kaempferol, naringenin, and hesperetin bind the pocket of S3, S2, S1′, and S2′. In the S3 pocket, the amino-acid residue is Ala115, Phe117, Gln13, Pro111, Thr12, Leu114, Ser219; in the S2 pocket is Met289; in the S1 pocket are Thr295, Leu213, Asp215, Gly217, Ile291, Ser76; and in S1′ pocket is Gln128, Gly34, yr75Ser35, Arg74, Ile130.

Several interactions exist between each ligand and the amino-acid residues of the protein renin. The difference in the interaction is due to the differences in the structure of each ligand. Overall, all three compounds interact with amino-acid residues that play an essential role in renin binding.

The SwissADME web tool may compute essential physicochemical, pharmacokinetic, druglike, and related characteristics for one or more substances.[14] The analysis of pharmacokinetic profiles and the search for physical and chemical properties showed that the seven compounds violated 3 of the 5 Lipinski rules, while aliskiren violated 1 [Table 4]. Hesperitin, kaempferol, and naringenin had similarities with aliskiren on the amino-acid residues in the renin-binding pocket. However, based on pharmacokinetic analysis, the three compounds had an oral pharmacokinetic profile that was not as good as aliskiren. The Lipinski rule of five is useful for identifying druglike compounds and those that are not. If a molecule satisfies two or more of the following criteria about druglikeness, there is a significant chance that it will be successful or unsuccessful in the pharmaceutical industry. Low molecular weight (<500 Dalton); high lipophilicity (logP <5); 5 or fewer hydrogen-bond donors, 10 or fewer hydrogen-bond acceptors, and molar refractivity ought to range from 40 to 130.[15]

CONCLUSION

Luteolin, quercetin, kaempferol, myricetin, naringenin, hesperetin, and epicatechin have potential as renin inhibitors with affinity energy values lower than those of aliskiren of −9.3; −9.3; −10.0; −9.2; −9.9; −9.3; and −9.7 kcal/mol. Hesperitin, kaempferol, and naringenin had similarities with aliskiren on the amino-acid residues in the renin-binding pocket. However, based on pharmacokinetic analysis, the three compounds had an oral pharmacokinetic profile that was not as good as aliskiren.

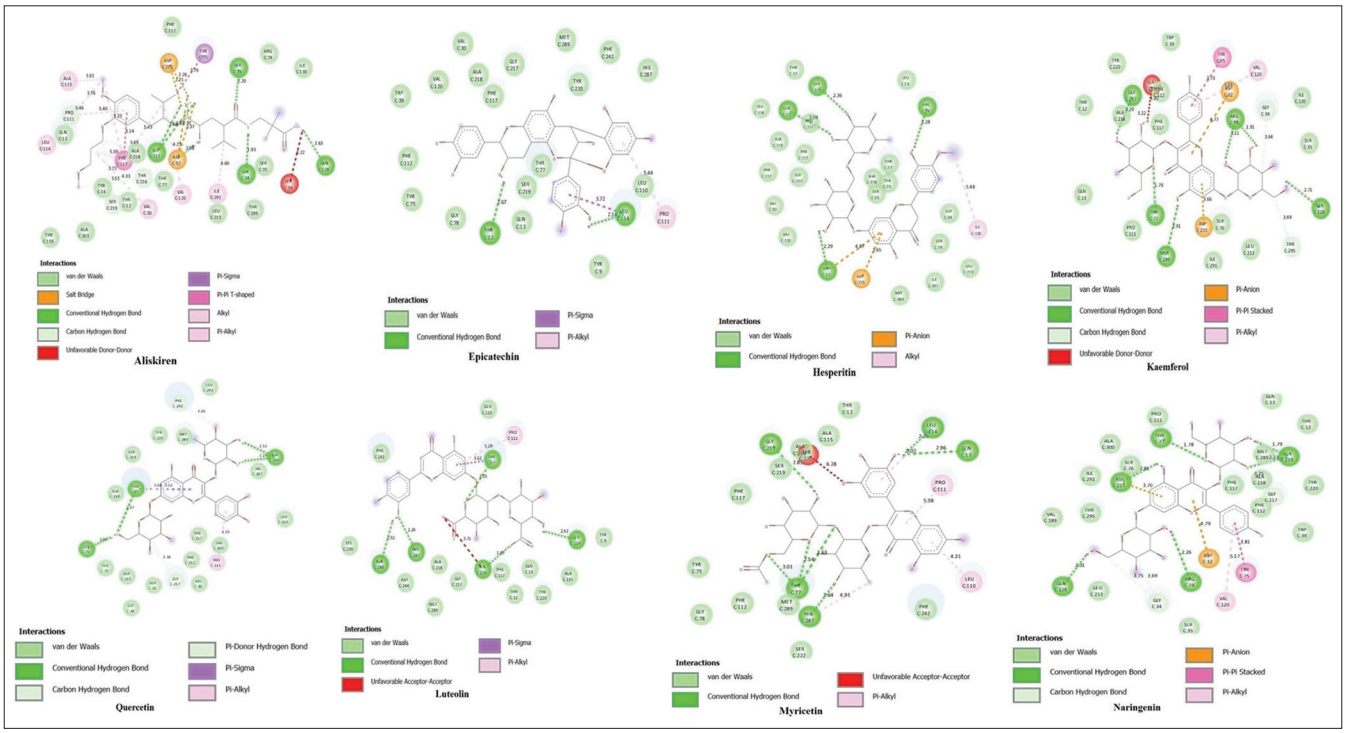


Figure 3: Three dimension visualization of the test ligand and aliskiren

Table 4: Native ligand (aliskiren) and test ligand pharmacokinetics characteristics

Ligands	Mol mass	NB	HDn	HAc	TPSA (A)	log *P*	GI Abs	3BP	NLVR	BA	PgP substrat
Aliskiren	551.76	20	4	7	146.13	4.15	Low	No	1	0.55	Yes
Epicatechin	576.50	2	9	12	209.76	1.88	Low	No	3	0.17	No
Hesperitin	610.56	7	8	15	234.29	2.6	Low	No	3	0.17	Yes
Kaempferol	610.52	7	10	16	269.43	2.34	Low	No	3	0.17	Yes
Quersetin	610.52	6	10	16	269.34	2.59	Low	No	3	0.17	Yes
Luteolin	636.47	7	8	18	309.27	1.70	Low	No	3	0.11	Yes
Myricetin	667.55	8	9	18	298.56	2.43	Low	No	3	0.11	Yes
Naringenin	580.54	8	6	12	192.44	2.24	Low	No	3	0.17	No

Mol Weight: Molecular mass (g/mol), NB: Number of bonds that can rotate, HDn: Number of hydrogen-bond donors, HAc: Number of acceptors for hydrogen bonds, TPSA: Topological polar surface area (Å2), log P: Octanol/water partition coefficient predicted, GI Abs: Gastrointestinal absorption, 3BP: Blood-brain barrier permeation, NLVR: Number of violations of the Lipinski rule, BA: Score for bioavailability; PgP: P-Glycoprotein

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Nil.

Conflicts of interest
There are no conflicts of interest.

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