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## ***In silico* docking analysis of the compounds of orthosiphon stamineus for the nephroprotective activity**

**C. Maheswari, R. Venkatnarayanan, R. Manavalan, J. Sam Johnson, J. Subadradevi and P. Babu**

*RVS College of Pharmaceutical Sciences, Sulur, Coimbatore*

### **ABSTRACT**

The present study is aimed to evaluate the *In-silico* docking analysis of the compounds identified from the leaves of *Orthosiphon stamineus* for the Nephroprotective activity. Captopril is used as a standard and it is well-known for the Nephroprotective activity by inhibiting the enzyme known as Angiotensin Converting Enzyme (ACE). Compound 1- Eupatorin, Compound 2- Rosmarinic acid, Compound 3- Orthosiphol A, Compound 4- Sinenstein, Compound 7- 5-Hydroxy- 6,7,3,4-tetramethoxyflavone identified from the leaves of *Orthosiphon stamineus* have shown significant ACE receptor inhibitory activity. Of the 5 compounds Eupatorin (compound 1), Rosmarinic acid (compound 4) showed maximum ACE Receptor inhibition than the standard drug Captopril and have shown excellent Nephroprotective activity with better ADMET profiles.

**Keywords:** *Orthosiphon stamineus*, Nephroprotective activity, *In-silico* docking, ACE

### **INTRODUCTION**

The world's disease profile is changing, and chronic diseases now account for the majority of global morbidity and mortality, rather than infectious diseases. During the 20th century, infectious diseases were the major cause of death and disability. However in this century, non communicable, non infectious chronic diseases such as hypertension, liver failure and kidney failure have become the major cause of mortality and morbidity around the world.

Renal failure is a condition in which the kidneys are fail to remove metabolic end-products from the blood and regulate the fluid, electrolyte, and pH balance of the extracellular fluids. The underlying cause may be renal disease, systemic disease, or urologic defects of non renal origin. Renal failure can occur as an acute or a chronic disorder. Acute renal failure is abrupt in onset and often is reversible if recognized early and treated appropriately. In contrast, chronic renal failure is the end result of irreparable damage to the kidneys. It develops slowly, usually over the course of a number of years. Acute renal failure is caused by conditions that produce an acute shutdown in renal function. It can result from decreased blood flow to the kidney (pre renal failure), disorders that interfere with the elimination of urine from the kidney (post renal failure), or disorders that disrupt the structures in the kidney (intrinsic or intra renal failure). Acute renal failure is classified as pre renal, post renal, or intra renal in origin. Unlike acute renal failure, chronic renal failure represents progressive and irreversible destruction of kidney structures. Chronic renal failure represents the end result of conditions that greatly reduce renal function by destroying renal nephrons and producing a marked decrease in the glomerular filtration rate (GFR). Signs of renal failure begin to appear as renal function moves from renal insufficiency (GFR 50% to 20% normal), to renal failure (20% to 5% normal), to end-stage renal disease.

Plants and other living organisms have great potential to treat human disease. There are two distinct types of biomedical research that seek to develop this potential. One type of research explores the value of medicinal plants as traditionally used, which constitute the only available medicines for most people in poor countries. Studies of

these plants have the potential to determine which plants are most potent, optimize dosages and dose forms, and identify safety risks. Another type of research uses bioassays to identify single molecules from plants that have interesting bioactivities in isolation and docking analysis might be useful for the confirmation of therapeutic activity of the compounds identified from the medicinal plants.

Computational Biology and bioinformatics have the potential not only of speeding up the drug discovery process thus reducing the costs, but also of changing the way drugs are designed. Rational drug design (RDD) helps to facilitate and speedup the drug designing process, which involves variety of methods to identify novel compounds. One such method is the docking of the drug molecule with the receptor (target). The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor and docking is the process by which two molecules fit together in 3D space.

*Orthosiphon stamineus Benth* known as kidney tea or java tea, is a genus of plants in the Lamiaceae family native to Southeast Asia. It is an herbaceous shrub which grows to a height of 1.5 m (4.9 ft). *Orthosiphon* is a popular garden plant because of its unique flower, which is white and bluish with filaments resembling a cat's whiskers and leaves has been shown to be a mild diuretic, kidney and bladder stones and infections of the urinary tract. The essential oil of the drug, which contains sesquiterpenes, is Antimicrobial. In folk medicine, it is used for the above conditions and also for gout and Rheumatism [13-17]. A Bioactive compounds has been already reported from the leaves of *Orthosiphon stamineus* [1-5, 12] and based on the extensive medicinal claims of leaves of *Orthosiphon stamineus* for the nephroprotective activity, The aim of the present study is designed to evaluate the insilico docking analysis of the compounds identified from the leaves of *Orthosiphon stamineus* for the Nephroprotective activity to confirm the therapeutic effect of the leaves of this plant.

## MATERIALS AND METHODS

### Compounds

The following compound were identified from the leaves of *Orthosiphon stamineus* plant

Compound 1- Eupatorin

Compound 2- Rosmarinic acid

Compound 3- Orthosiphol A

Compound 4- Sinenstein

Compound 5- Cichoric acid

Compound 6- Betulinic acid

Compound 7- 5-Hydroxy- 6,7,3,4-tetramethoxyflavone

Compound 8-  $\beta$ -Sitosterol

The steps involved in docking are as follows:

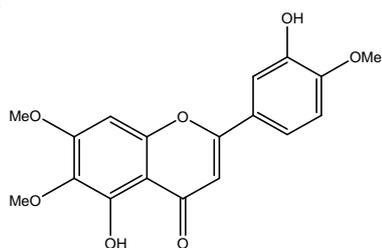
### SOFTWARE'S HANDLED

1. GLIDE module version 5.9., mastero 9.4
2. Qik prop -3.6 -Schrödinger, LLC, New York, NY, 2013- docking123<sup>10,11</sup>
3. Swiss PDB viewer-4.04 – protein viewer
4. Pymol viewer 1.3 – image viewer
5. Marveen sketch 5.5 – drawing ligand structure

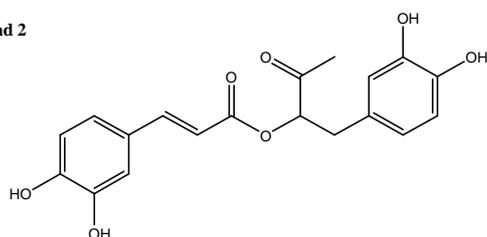
### Ligand structure

The chemical structure of each ligand is drawn using build module

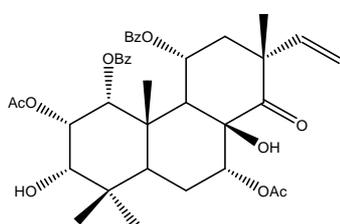
Compound 1



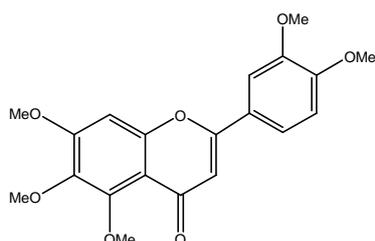
Compound 2



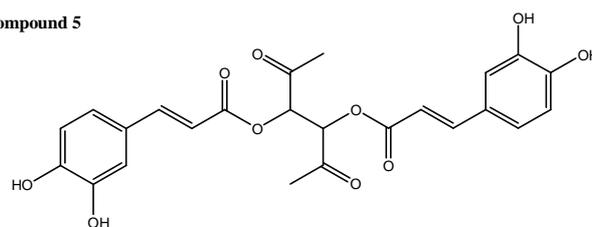
Compound 3



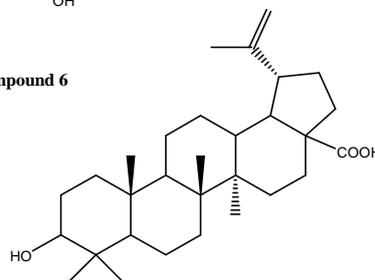
Compound 4



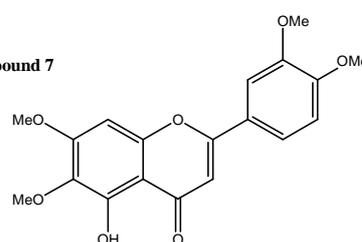
Compound 5



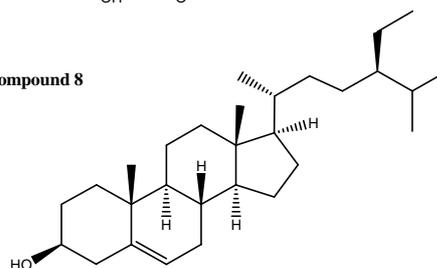
Compound 6



Compound 7



Compound 8



### ADME property screening

The Qik Prop tool [10] from Schrodinger helps to screen the molecules for their drug like property by using lipinski's rule of 5 [11]. It is a (ADME) prediction program in the Schrodinger's Maestro. It predicts the absorption, distribution, metabolism, and excretion (ADME) physically significant descriptors and pharmaceutically relevant properties of organic molecules

### Docking Procedure

Docking studies of 8 compounds were performed using 3 proteins obtained from the RCSB Protein Data Bank, <http://www.rcsb.org/pdb>. Experiments were performed using the program GLIDE (Grid-based Ligand Docking with Energetic) module version 5.9, Schrödinger, LLC, New York, NY, 2013 (Schrodinger Inc.) [9]. Coordinates of the full-length substrate- complexed dimmer were prepared for Glide 5.9 calculations by running the protein preparation wizard. The p-prep script produces a new receptor file in which all residues are neutralized except those that are relatively close to the ligand (if the protein is complexed with a ligand) or form salt bridges. The impref script runs a series of restrained impact energy minimizations using the Impact utility. Minimizations were run until the average root mean square deviation (rmsd) of the non-hydrogen atoms reached 0.3Å. Glide uses two boxes that share a common centre to organize its calculations: a larger enclosing box and a smaller binding box. The grids themselves are calculated within the space defined by the enclosing box. The binding box defines the space through which the centre of the defined ligand will be allowed to move during docking calculations. It provides a measure of the effective size of the search space. The only requirement on the enclosing box is that it be large enough to contain all ligand atoms, even when the ligand centre is placed at an edge or vertex of the binding box [6,7,8].

## RESULTS AND DISCUSSION

The ADME properties of the ligands were predicted using QikProp. The compounds prepared were subjected to drug-likeness filter. The acceptance criteria of the filter includes

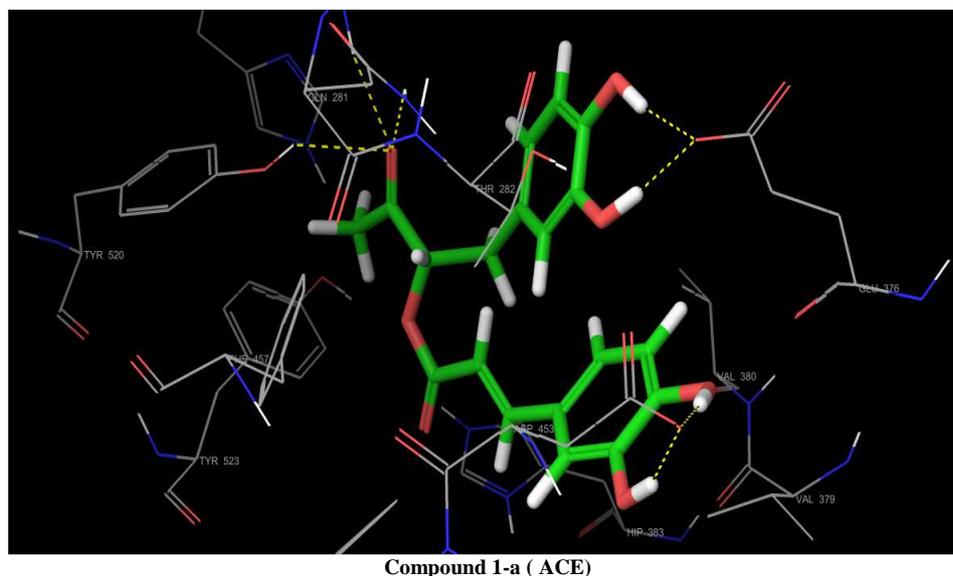
Molecular weight (< 500), QPPMDCK (<25-poor, > 500 good, Q Plog BB (-3.0 to 1.2), Donar HB (0-6), Metabolism (1-8), Accept HB (2-20), Log P Value o/w (-2.0 to 6.5), CNS (-2 to +2), % Human Oral Absorption (80% high <25% poor), Violation of Rule Of Five (Max 4), QP P Caco (< 25-poor, > 500-Good), PSA (7-200), Q P log S (-6.5 to 0.5), Violation of Rule Of Three (Max 3). All the ligands confirmed to the above mentioned acceptance criteria and they were evaluated for docking using GLIDE software.

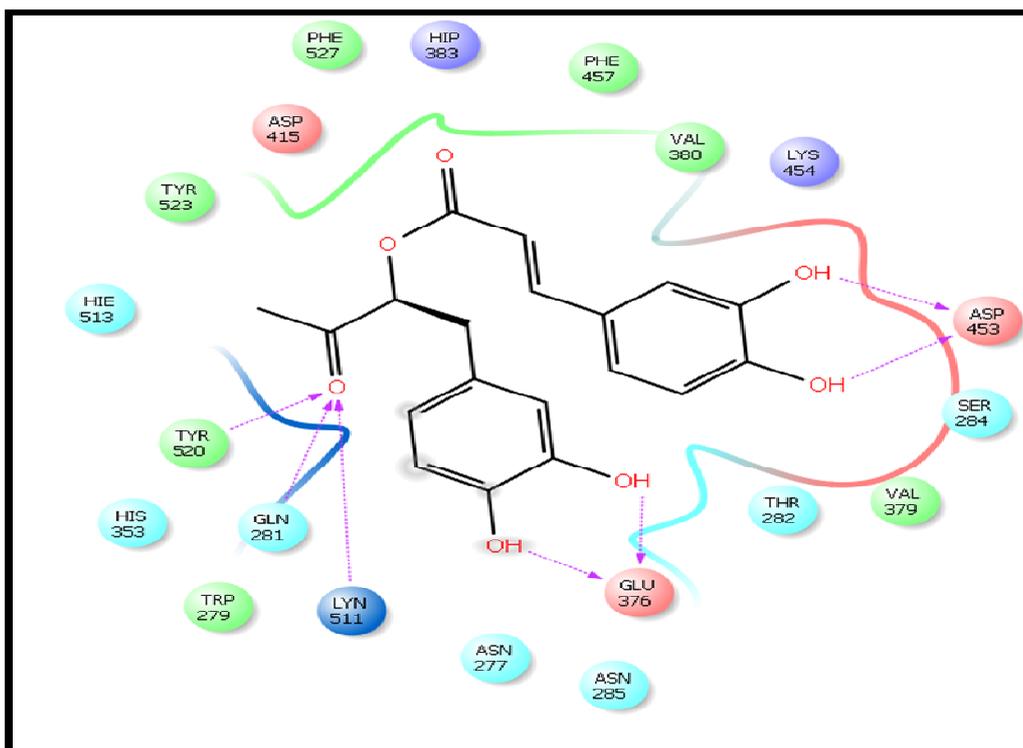
GLIDE receptor grid was generated to determine the size of the active site. The most probable orientation of the ligands in the binding pocket is identified and a scoring function is used to quantify the strength of the interaction a molecule can make in a particular orientation. In order to provide better correlation between good poses and good scores, the GLIDE XP precision was favoured over the standard mode. The docking analysis was done for the ligands with the target proteins PXR and NF- $\kappa$ B using the docking software GLIDE and the docked images are shown in figure 1(a & b), 2 (a & b), 3 (a & b), 4 (a & b), 5 (a & b), and 6 (a & b). The structures docked by GLIDE are generally ranked according to the GLIDE Scoring Function (more negative). In the present study, extra precision GLIDE docking procedure was validated by removing the inhibitor compound with NF- $\kappa$ B protein has been analyzed from the G-score, GLIDE energy and H-bonds. The docking result of these ligands are given (Table 1). The interaction energy includes vander waals energy, electrostatic energy, as well as intermolecular hydrogen bonding were calculated for each minimized complex. Captopril is used as standard and it is well-known for nephroprotective activity by inhibiting the ACE enzyme.

In the present study, in-silico docking was carried out for the compounds present in *Orthosiphon stamineus* in comparison with standard Captopril against ACE protein. Compounds 1,2,3,4 and 7 have shown significant ACE Receptor inhibitory activity. Of the 5 compounds Eupatorin (compound 1), Rosmarinic acid (compound 4) showed maximum ACE Receptor inhibition than the standard drug Captopril have shown excellent Nephroprotective activity with better ADMET profiles (Table 2)

### Docking images (a) and 3D images (b) of designed compounds showing maximum activity against ACE Receptor

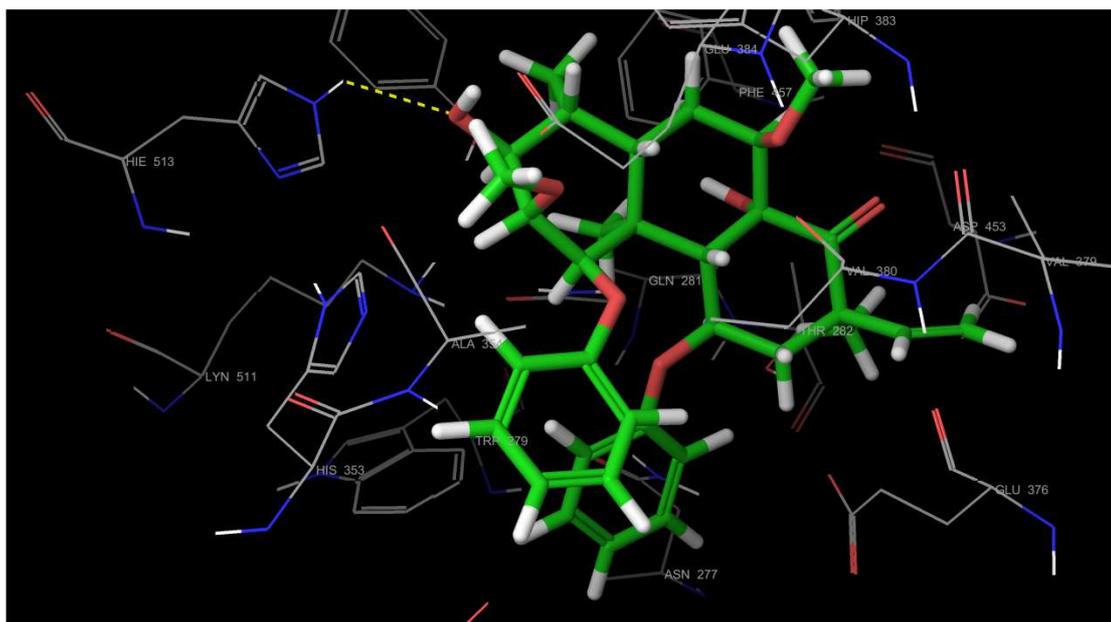
FIGURE- 1



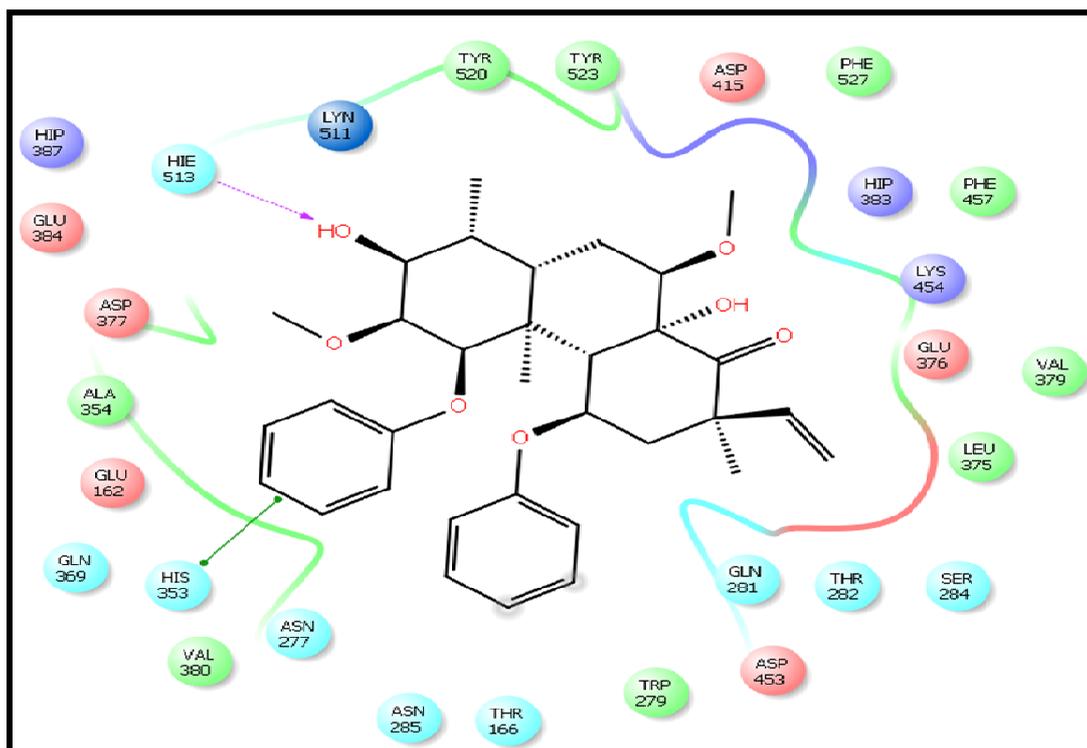


Compound 1-b (ACE)

FIGURE-2

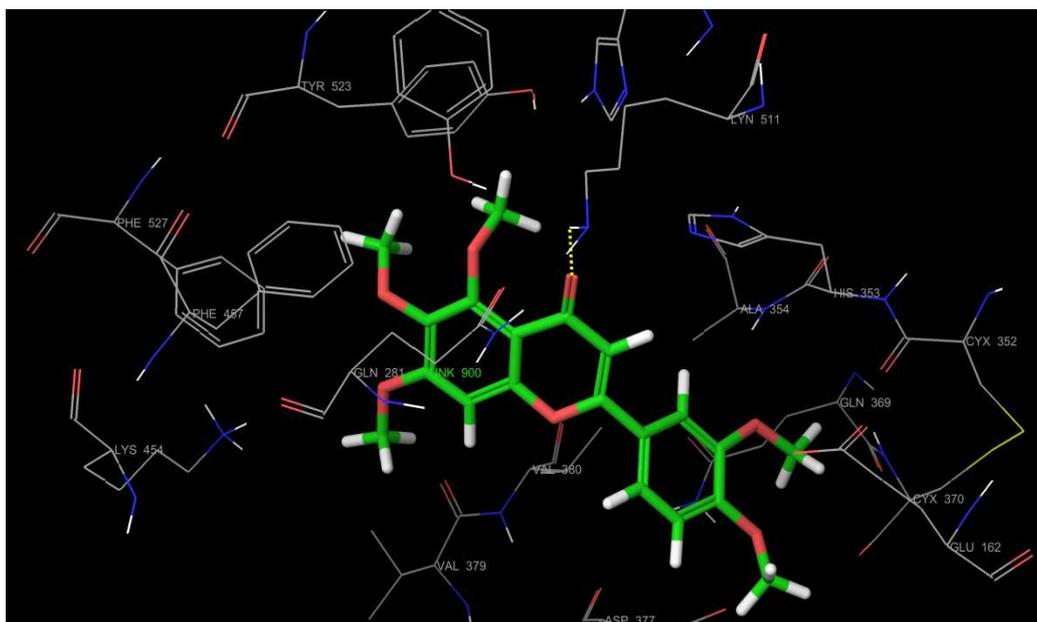


Compound 2-a (ACE)

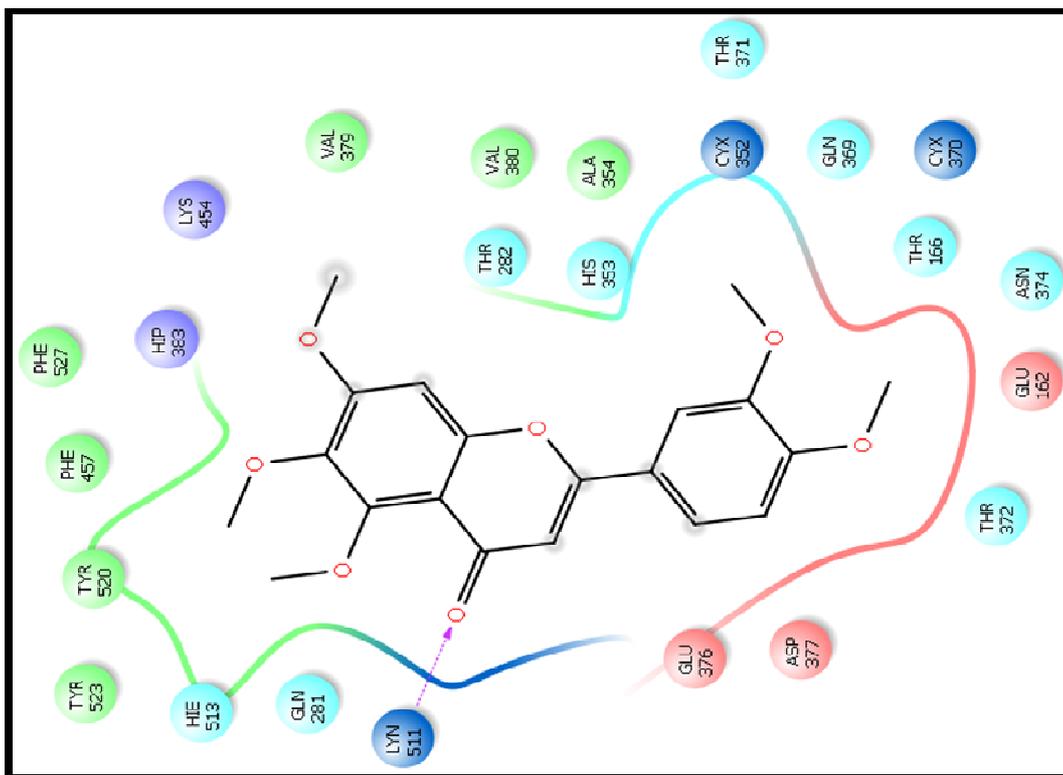


Compound 2-b (ACE)

FIGURE 3

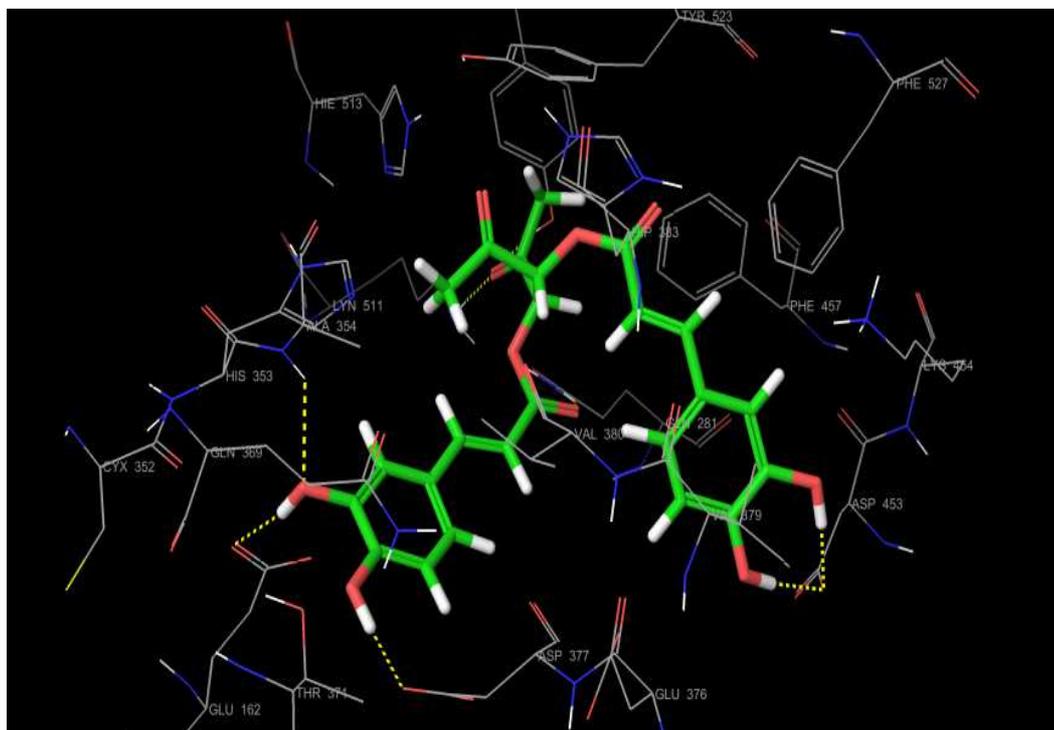


Compound 3-a (ACE)

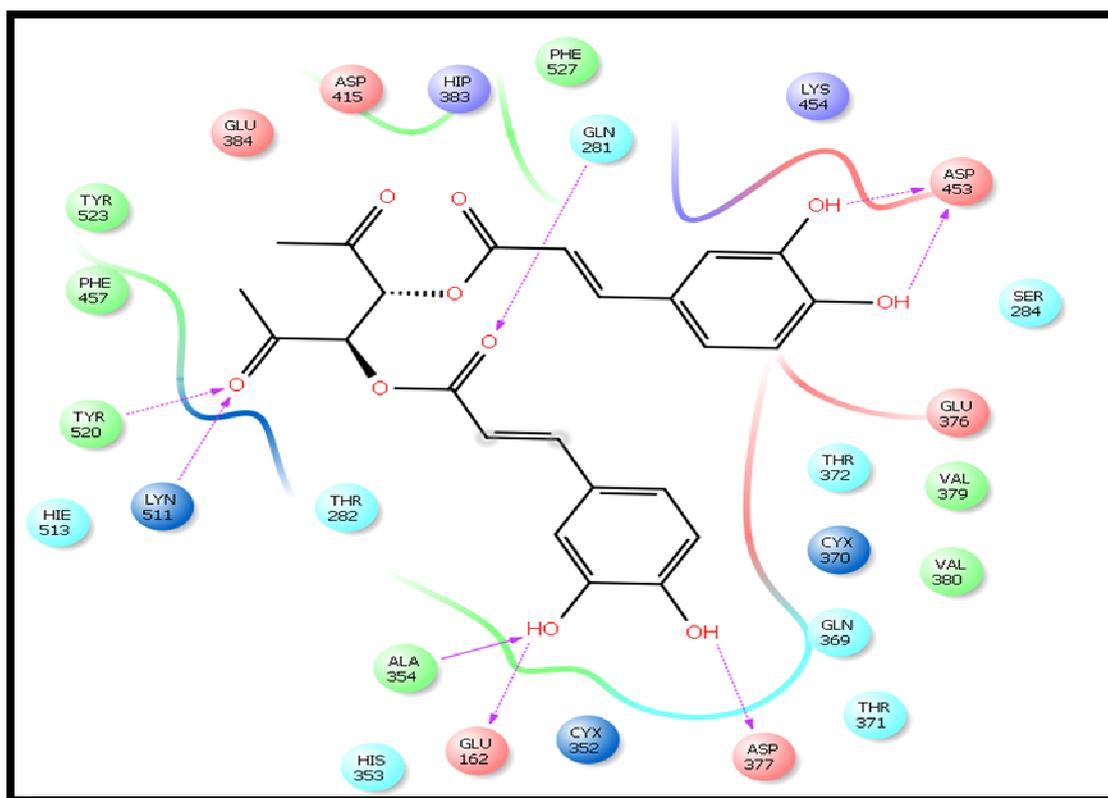


Compound 3-b (ACE)

FIGURE 4

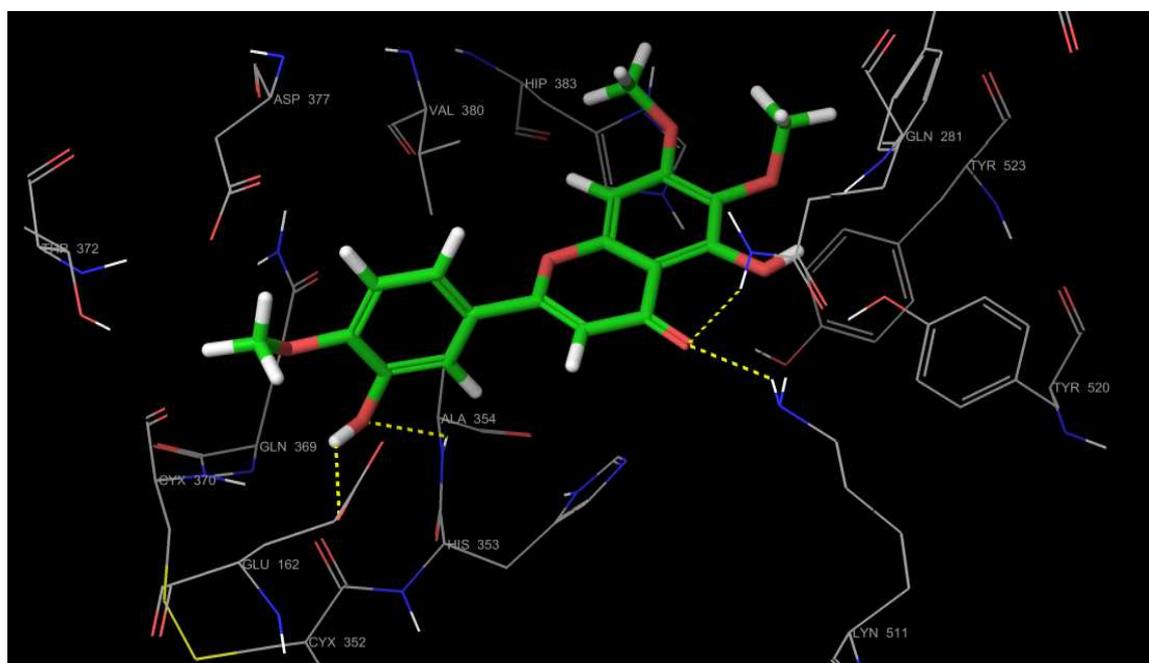


Compound 4-a (ACE)



Compound 4-b (ACE)

FIGURE-5



Compound 7-a( ACE)



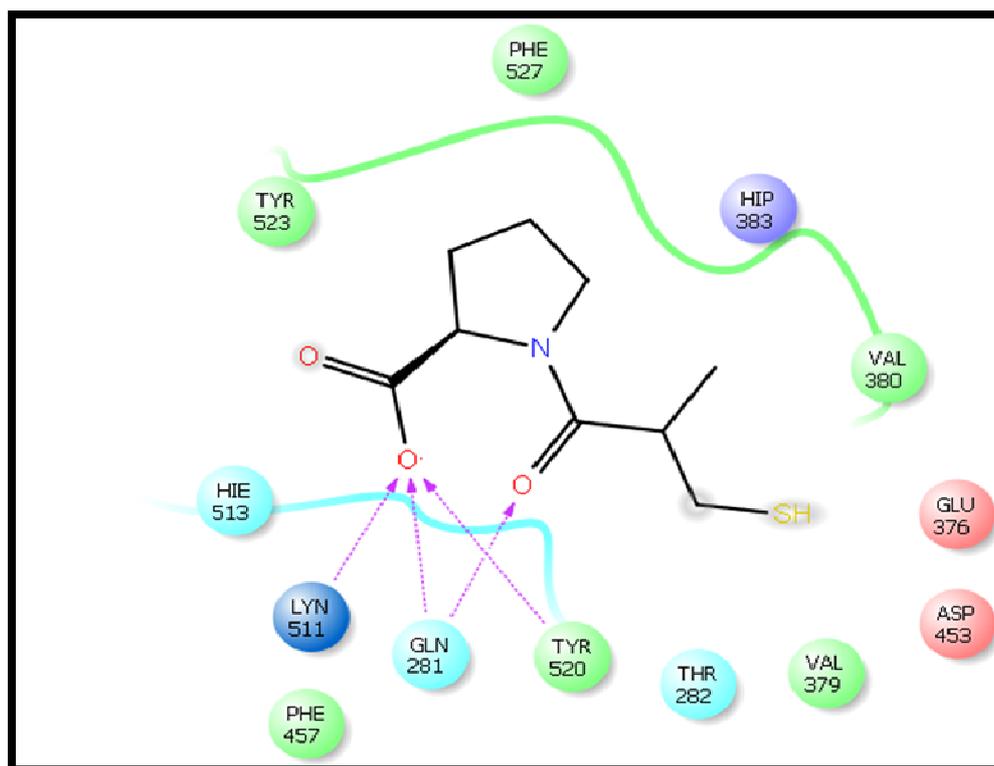


FIG 6 STD Captopril-b (ACE)

TABLE 1 Summary of GLIDE result of ligands against ACE for Nephroprotective activity

PARAMETERS	CP1	CP2	CP3	CP4	CP5	CP6	CP7	CP8	Captopril
Glide Score	-9.909692	-5.232298	-5.227103	-11.340965	-4.226468	-4.276425	-5.445692	-4.748829	-5.25261
Glide Energy	-56.301081	-39.744262	-43.157097	-73.171827	-32.071475	-35.841348	-45.370877	-18.239206	-29.7575

TABLE 2 PHARMACOKINETIC PARAMETERS WITH THEIR OPTIMUM RANGE IMPORTANT FOR CNS ACTIVITY AND ORAL BIOAVAILABILITY OBTAINED BY QIKPROP TOOL

PARAMETERS	CP1	CP2	CP3	CP4	CP5	CP6	CP7	CP8	Captopril
Molecular weight (< 500)	358.34	550.691	372.374	470.432	456.707	358.347	344.32	414.717	.282
QPPMDCK (<25-poor, > 500 good)	317.807	305.78	6.183	1178.967	2130.831	1.747	207.689	787.593	1860.521
Violation of Rule Of Three (Max 3)	0	0	1	1	0	1	1	0	1
Donar HB (0-6)	4	2	0	4	2	0	1	1	1
Metabolism (1-8)	6	2	5	6	3	5	5	3	3
Accept HB (2-20)	7	9.35	6.25	11	3.7	5.25	5.25	1.7	4.5
Log P Value o/w (-2.0 to 6.5)	1.316	5.602	3.551	1.341	6.06	3.468	2.892	7.538	0.342
CNS (-2 to +2)	-2	-1	0	-2	-1	0	-1	0	-1
% Human Oral Absorption (80% high <25% poor)	56.829	94.616	100	48.732	100	100	94.876	100	68.071
N and O (2-15)	4	7	7	7	7	10	3	7	1
Violation of Rule Of Five (Max 4)	0	2	0	0	1	0	0	1	0
QP PCaco (< 25-poor, > 500-Good)	153.425	640.757	17.349	2233.211	3861.378	5.388	358.63	1537.588	3405.935
PSA (7-200)	149.946	74.444	68.341	204.996	57.75	83.04	94.021	22.273	72.037
Q Plog S (-6.5 to 0.5)	-3.074	-6.16	-4.296	-4.44	-6.659	-4.346	-4.339	-8.578	-1.726
Q Plog BB (-3.0 to 1.2)	-0.418	-0.943	-3.1	-0.642	-0.167	-4.254	-0.383	-0.569	-0.352

## CONCLUSION

Based on the docking analysis the study concluded that the leaves of *Orthosiphon stamineus* is potential for the Nephroprotective activity by inhibiting ACE Receptor with better ADMET profiles.

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