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Structure-Based Pharmacophore Design and Natural Bond orbital analysis of Angiotensin Converting Enzyme inhibitors

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ABSTRACT: Hypertension and congestive heart failures are becoming epidemic throughout the world. Angiotensin Converting Enzyme (ACE), a metallo-peptidase is the best known important drug target in the treatment of hypertension and responds to broad range ACE inhibitors such as Captopril. Though there are many synthetic drugs that are being used as ACE inhibitors, the usage of natural compounds has its significance with less adverse effects. In this regard, many phytochemical compounds including alkaloids and flavonoids has been reported with anti-hypertensive activity. In this connections, the present study is focused on determining the anti-hypertensive actively of certain phytochemical compounds and synthetic drugs through docking studies and to explore their pharmacophoric features. The docking study implies that rosemarinic acid was relatively better that that of Standard drugs Lisinopril and Captropril. The pharmacophore modelling, validation and screening studies on rosemarinic acid along with Lisinopril and Captropril resulted in two compounds from Maybridge compound database (CD 01374 and CD 01278). Also the Density function theory (DFT) studies on these compounds explained the charge transfer (HOMO–LUMO energy gap of 2.90 eV) interactions that are taking place within the molecule through strong N–H···N and N–H···O hydrogen bonding is essential for the bioactivity of these compounds. Thus the finding of this study clearly emphasized that the rosemarinic acid could significantly possess better ACE inhibition activity and could be an alternative therapeutic agent to replace the drugs with severe side effects.

Keywords: *Angiotensin Converting Enzyme; ACE inhibitors; Pharmacophore; Lisinopril; Captropril; rosemarinic acid;*

1. INTRODUCTION

In recent years, cardiovascular diseases have become a serious problem worldwide. The World Health Organization has reported an increase in the number of patients suffering from this disease. Currently, existing treatments for high blood pressure are not very effective and are generally uncomfortable for patients. This relies in that the patient need to have a very strict control in the dosage and in the moment of the administration of the drug [1]. And also some patients have an unfavorable response after the administration, leading them to a fast blood pressure reduce. One of the most widely used compounds for the treatment of hypertension is captopril. Like many others on the market, this drug was designed with computational tools. Over the last few decades, computational studies, together with rational drug design, have become a critical part in the development of new drugs. Currently, cardiovascular diseases are a serious health problem worldwide. One example of cardiovascular disease is arterial hypertension, which is defined as increased systolic pressure, diastolic pressure, or both [2].

Hypertension is a silent, asymptomatic disease, and as a result, not many people know that they suffer from it. Hypertension is an important risk factor, contributing to other cardiovascular diseases such as blood vessel disorders, coronary heart disease, aortic aneurysm, stroke, etc [3]. Cardiac arrhythmia is another cardiovascular problem. An arrhythmia is any disorder of the heart rate that may cause stroke. Heart rhythm disorders may be caused by genetic factors or occur when the heart muscle (myocardium) is damaged, sometimes by hypertension [4]. Raised blood pressure, especially systolic pressure (hypertension), confers a significant cardiovascular risk and

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public health concern and should be actively treated.

One of the major systems involved in the elevation of the pressure is the renin–angiotensin system (RAS) and subsequently its inhibition will have beneficial effects to lower blood pressure and improve cardiovascular health [5]. The RAS is regulated by a series of highly specific enzymatic reactions. The first enzymatic reaction in the pathway starts with renal production of renin that cleaves angiotensinogen to generate angiotensin I. Angiotensin I is then cleaved by angiotensin–converting enzyme (ACE) to generate the active peptide vasoconstrictive hormone angiotensin II.

In the last three decades, several intensive efforts have been conducted into researching the antihypertensive therapeutic values of medicinal plants [6-8]. While compared to allopathic treatment, medicinal and bioactive plants have become a vital resource for the treatment of heart problems [9]. Nearly 80% of the global population including many developed and developing countries prefers to use natural medicines, due to their minimal side effects and better usage ability of humans [10]. In this scenario, the present study was emphasized to provide the insights of alkaloid from various medicinal plant source and to explore their binding mechanism within the active site of ACE, explore the chemical features that ascertain the ACE inhibitors activity through pharmachophore designing and to understand the chemical entities through DFT studies which might pave path to design of novel ACE inhibitors with potential inhibition activity.

2. METHODOLOGY

2.1 Target Selection

The X-ray Crystal Structure of Human Angiotensin Converting Enzyme complexedwith Lisinopril (PDB ID: 1O86) [11] was retrieved from Protein Databank [12]. The protein energy was minimized through 20 steps of steepest descent and conjugate gradient by using GROMOS [13] of SwissPDBviewer and final energy minimized model used for further Docking studies.

2.2 Ligand selection

The SMILES notation of eighteen phytochemical compounds including alkaloids and flavonoids from various medicinal plants were obtained by drawing their 2D structures in ACD-Chemsketch (Version 12) (www.acdlabs.com). The 3D structures of these compounds were generated and converted into SDF format by using 'Online SMILES convertor and Structure file generator' server [15].

2.3 Binding site prediction

The amino acid residues in binding site of ACE protein are defined by using the reference Ligand of Angiotensin Converting Enzyme complexed with Lisinopril [11]. The acid residues within 6 Å radius of reference Ligand was included in the predicted binding site by using LeadIT (Version 2.1.9) [16].

2.4 Virtual Screening

The 3D structures of all the selected eighteen phyotchemical compounds and two ACE inhibitors were virtually screened to reveal their binding efficiencies through docking in the predicted binding site of ACE using FlexX module of LeadIT. The docking was performed with the default parameters such as triangle matching base placements, zero full score and No score contributions and threshold for full score and no score contributions of 30 & 70 respectively, Clash handling values of 2.9 Å and 0.6 for protein ligand clashes with maximum allowed overlap volume and intra-ligand clash factors while considering the hydrogen in internal clash tests and 200 as the default docking values for maximum number of solutions per iteration and also per fragmentations [17].

2.5 Docking interactions

The docking interactions revealing H-bond and van-der Waal forces among the phytochemical compounds and the amino acid residues of ACE were analyzed by using pose-view module of LeadIT.

2.6 Pharmacophore modeling and 3D database Screening

The pharmacophore model was generated by using the Pharamacophore option of discovery studio software (Accelrys Software Inc.) The best docked ACE inhibitor was used as training compound for the generation of a Pharamacophore by using option Auto Pharmacophore Generation which considers the Hydrogen bond acceptor (HB_ACCEPTOR), Hydrogen bond donor (HB_DONOR), Hydrophobic feature (HYDROPHOBIC), Negative ionizable feature (NEG_IONIZABLE), Positive ionizable feature (POS_IONIZABLE) and Aromatic ring (RING_AROMATIC) feature types to generate a selective pharmacophore model from a single ligand. The Principal value of 2 and the Maxis set to the Training ligand which ensures that all of the chemical features in the compound should be will be considered in building the pharmacophore space. The Auto Pharmacophore Generation option enumerates a set of candidate pharmacophore models from the features and chooses the pharmacophore with the highest selectivity as predicted by a Genetic Function Approximation (GFA) model. Using this generated pharmacophore hypothesis, compound screening was performed against, Maybridge database (www.maybridge.com/) consisting of one lakh compounds and assessed the compounds matching the pharamacophore by considering the Fit Values.

2.7 DFT studies

The determination of the energy gap between HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbitals) could provide the chemical reactivity and kinetic stability of molecules. The molecules were optimized and proposed for theoretical calculations (DFT studies) by using Gaussian software. The chemical hardness, that reveals the compounds stability and reactivity are expressed as: $\eta = (-EHOMO + ELUMO)/2$. While, the escaping tendency of electrons from an equilibrium system is defined through electronic chemical potential (μ) of the compound as $\mu = (EHOMO + ELUMO)/2$. In extension to this, the stabilization in compound energy acquired through an additional electronic charge from the environment is measured by arriving its global electrophilicity expressed as $\omega = \mu\ 2/2\eta$ that significantly expressed the power of a ligand molecule.

3. RESULT AND DISCUSSION

3.1 Target

Considering the role of ACE in controlling the blood pressure and in conversion of angiotensin I to angiotensin II, the protein structure of Human Angiotensin Converting Enzyme complexed with Lisinopril (PDB ID: 1O86) (Figure.1) was retrieved from Protein Databank and used as receptor for further docking studies.

3.2 Ligands

The selected 16 Phytochemical compounds along with their Pubchem ID and their plant sources were given in Table 1. The two well known first class therapeutic drugs of ACE inhibitors such as Captopril and Lisinopril were considered as references for docking studies. The structures of these phytochemical compounds and standard drugs were shown in Figure.2.

Table 1. Selected phytochemical compounds and their plant sources

Pubchem ID	Compound	Plant Source
CID:44259992	Hibiscetin-3-glucoside	*Hibiscus sabdariffa* L.
CID: 12358401	Apigenin	*Allium sativum*
CID: 5315615	Rosemarinic acid	*Mentha spicata*
CID: 5280863	Kaempferol	*Allium sativum*
CID: 5280805	Rutin	*Sophora secundiflora*
CID: 5280445	Luteolin	*Allium sativum*
CID: 5280343	Quercetin	*Allium sativum*
CID: 1794427	Chlorogenic acid	*Calluna vulgaris*
CID: 689043	Caffeic acid	*Argania spinosa*
CID: 637542	Coumaric acid	*Solanum lycopersicum*
CID: 367141	Epicatechingallate	*Camellia sinensis*
CID: 162350	Isovitexin	*Camellia sinensis*
CID: 107905	Epicatechin	*Theobroma cacao*
CID: 73160	Catechin	*Theobroma cacao*
CID: 73073	Serpentine	*Rauwolfia serpentine*
CID: 932	Naringenein	*Solanum lycopersicum*

3.3 Virtual Screening

It is observed that all the compounds in the study exhibited theoretically encouraging docking scores. Among these selected 18 compounds, two compounds namely Rosemarinic acid and Caffeic acid showed relatively good binding affinity as compared to the standard ACE inhibitor Lisinopril, which exhibited the dock score of -33.8026 kJ/mol. While, other eight compounds exhibited higher binding affinity scores when compared to Captopril (-28.0001 kJ/mol). Whereas the other six compounds such as Kaempferol (-27.3849 kJ/mol), Apigenin (-27.2702 kJ/mol), Catechin (-26.7584 kJ/mol), Serpentine (-25.1353 kJ/mol), Hibiscetin-3-glucoside (-23.9487 kJ/mol) and Naringenein (-23.3107 kJ/mol) exhibited relatively poor dock score when compared to that of the standard drugs emphasized in this study.

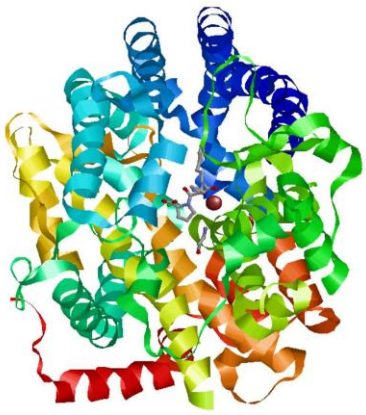


Figure 1. The protein structure of Human Angiotensin Converting Enzyme complexed with Lisinopril (PDB ID: 1O86)

Table 2. Docking interactions of the phytochemical compounds with higher docking affinities in comparison with Captopril

COMPOUNDS PUBCHEM ID								
44093	**637542**	**367141**	**162350**	**107905**	**5280805**	**5280445**	**5280343**	**1794427**
Gln281*	Gln281*	Gln281*	-	Glu281*	-	Gln281#	Gln281*	Gln281#
His353$	His353$	His353*	His353#	His353#	His353$	His353$	His353#	His353$
-	-	Ala354#	-	Ala354#	Ala354#	Ala354$	Ala354*	-
-	-	-	-	-	Ser355$	-	-	-
-	-	Val380$	-	Val380$	Val380$	-	-	-
His383$	His383$	His383#	His383#	His383#	His383#	His383$	His383#	His383*
-	-	-	Glu384*	-	Glu384*	Glu384*	-	Glu384*
-	His387*	-	His387*	-	-	His387*	His387*	His387*
Glu411*	-	-	Glu411*	-	-	Glu411*	-	-
-	-	-	Phe457$	-	Phe457$	Phe457$	Phe457$	-
Lys511*	Lys511*	-	-	-	Lys511*	Lys511*	Lys511*	Lys511*
His513#	His513$	His513#	His513#	-	His513#	-	-	His513$
Tyr520#	Tyr520*	-	-	-	Tyr520#	Tyr520*	Tyr520*	Tyr520*
Tyr523#	Tyr523$	Tyr523$	Tyr523$	Tyr523$	Tyr523$	Tyr523$	Tyr523$	Tyr523$
-	-	-	Phe527$	-	Phe527$	Phe527$	Phe527$	-
Docking Scores (kJ/mol)								
-28.0001	**-28.0932**	**-28.3753**	**-30.0155**	**-28.2712**	**-29.4384**	**-30.8914**	**-33.0149**	**-28.6159**

*Amino acid residues favouring H-bond interactions;
$ Amino acid residues favouring Non-bonded (Hydrophobic) interactions;
#Amino acid residues involved in both interactions.

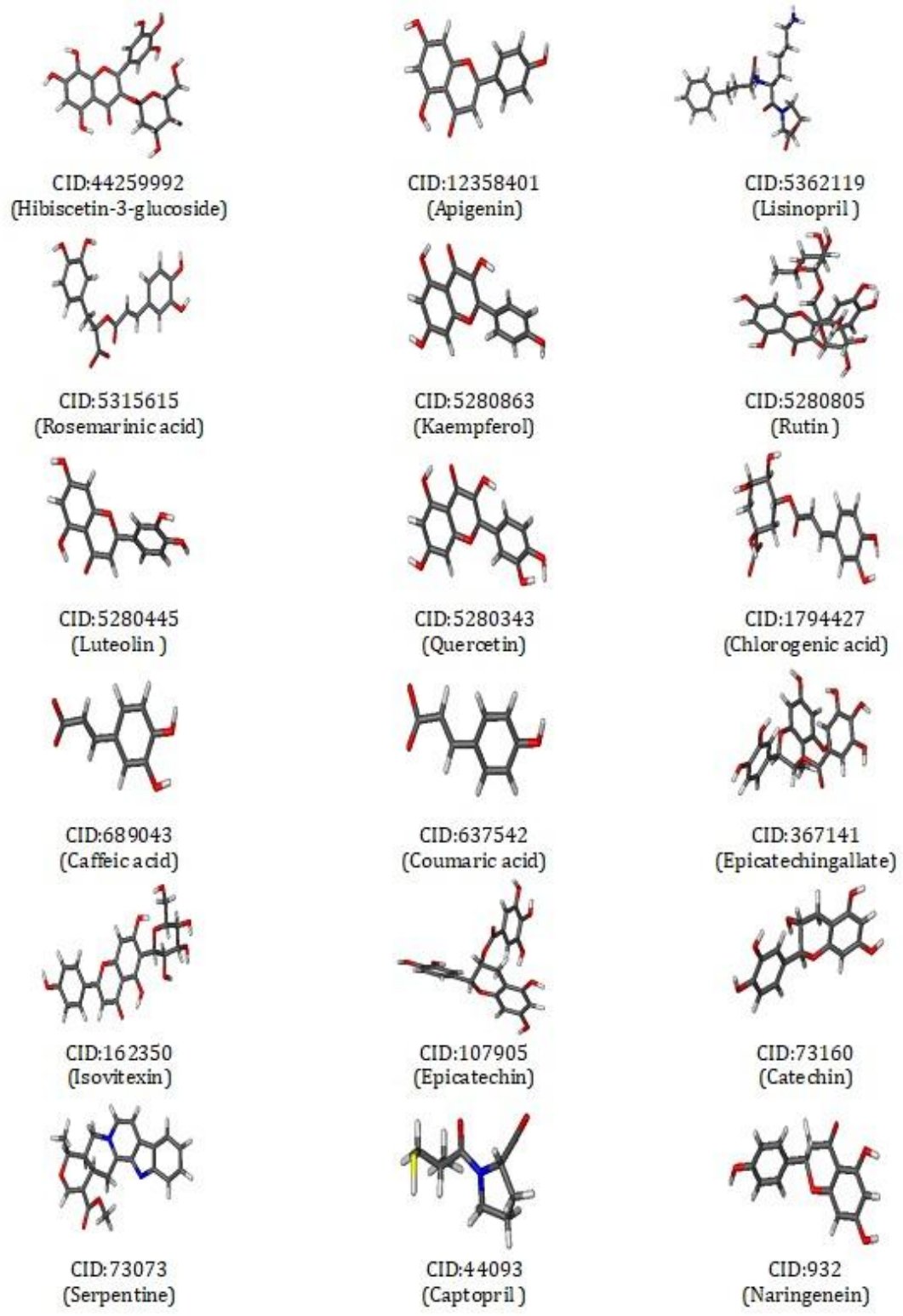
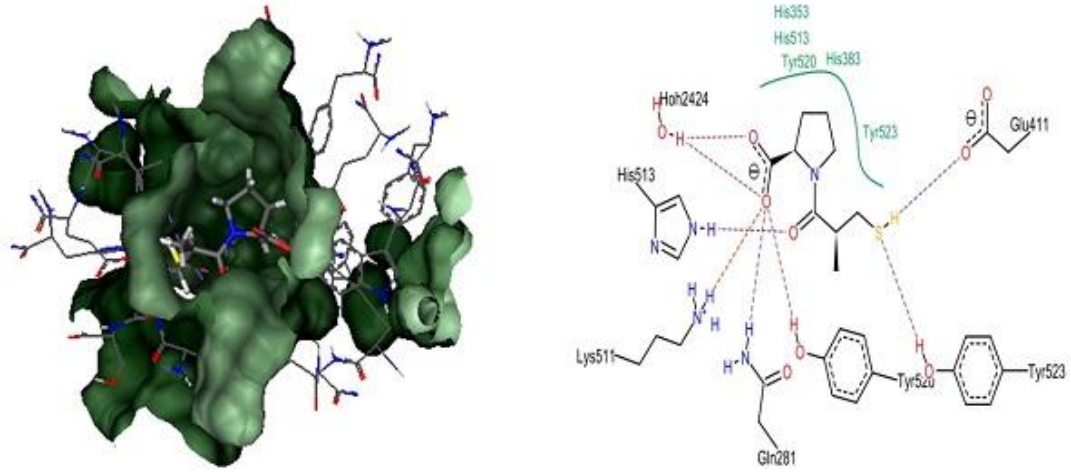
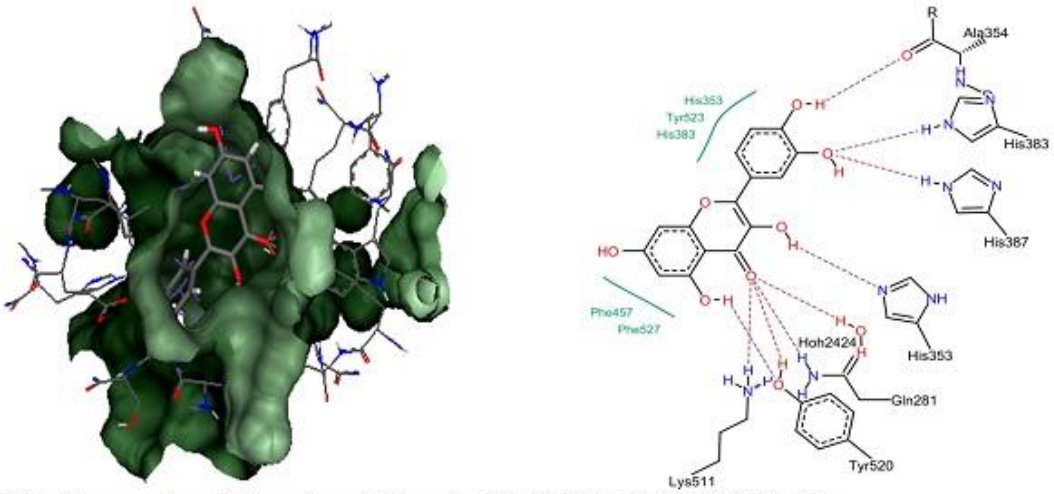


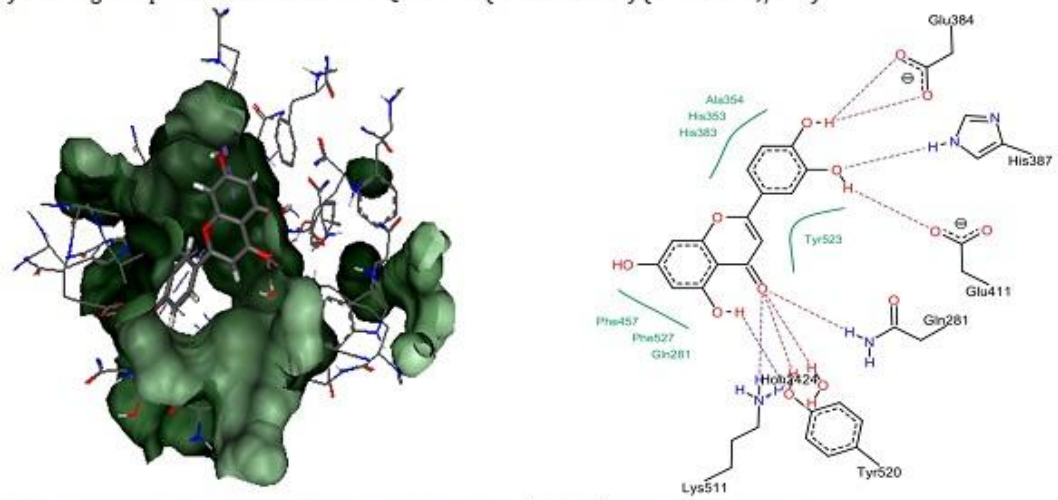
Figure 2. **Structures of phytochemical compounds and standard drugs**



(a) Docking complex and interactions of Captopril (CID: 44093) (-28.0001 kJ/mol)

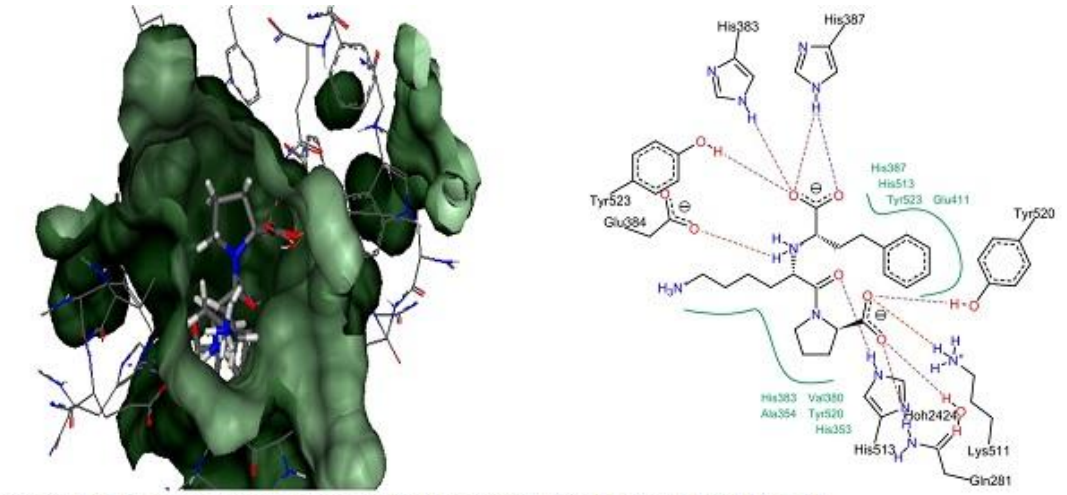


(b) Docking complex and interactions of Quercetin (CID: 5280343) (-33.0149 kJ/mol)

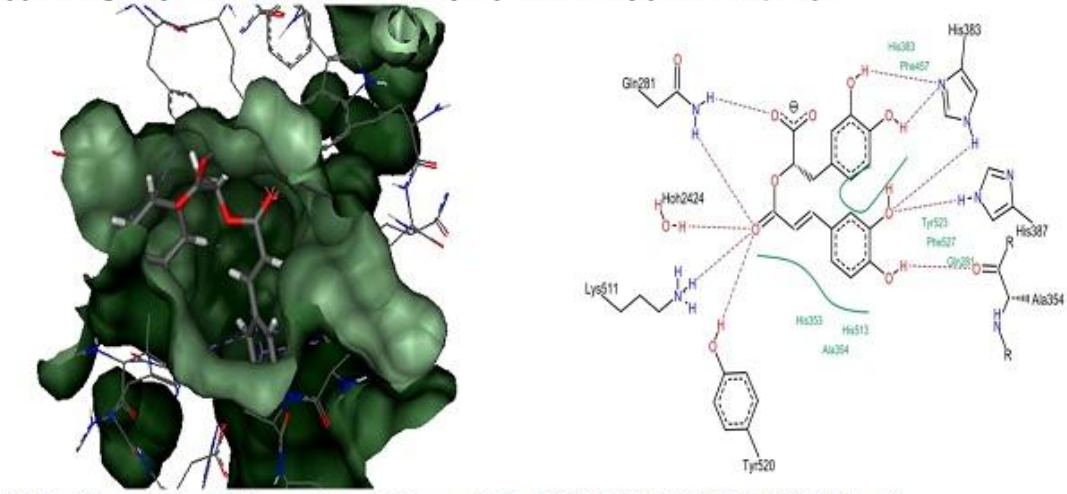


(c) Docking complex and interactions of Luteolin (CID: 5280445) (-30.8914 kJ/mol)

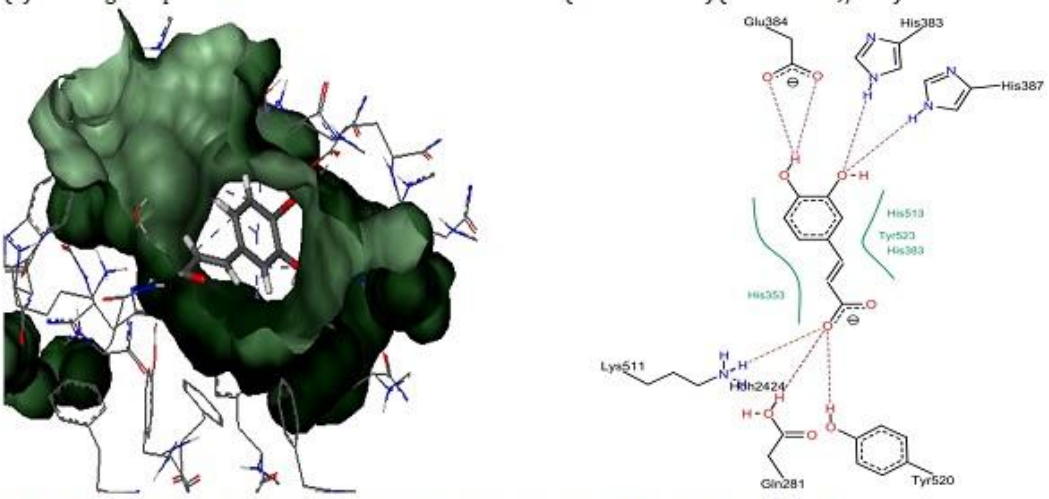
Figure 3. Docking interactions of the phytochemical compounds with higher docking affinities in comparison with Captopril



(a) Docking complex and interactions of Lisinopril (CID: 5362119) (-33.8026 kJ/mol)



(b) Docking complex and interactions of Rosemarinic acid (CID: 5315615) (--34.6473 kJ/mol)



(c) Docking complex and interactions of Caffeic acid (CID: 5280445) (-30.8914 kJ/mol)

Figure 4. Docking interactions of the phytochemical compounds with higher docking affinities in comparison with Lisinopril

Table 3. Docking interactions of the phytochemical compounds with higher docking affinities in comparison with Lisinopril

COMPOUNDS PUBCHEM ID		
5362119	**5315615**	**689043**
Gln281*	Gln281#	Gln281*
His353#	His353$	His353$
Ala354*	Ala354#	-
Ser355$	-	-
-	-	-
His383#	His383#	His383#
-	-	Glu384*
His387#	His387*	His387*
Glu411$	-	-
Phe457$	Phe457$	-
Lys511*	Lys511*	Lys511*
His513$	His513$	His513$
Tyr520#	Tyr520*	Tyr520*
Tyr523#	Tyr523$	Tyr523$
-	Phe527$	-
Docking Scores (kJ/mol)		
-33.8026	**-34.6473**	**-33.9872**

*Amino acid residues favouring H-bond interactions;
$ Amino acid residues favouring Non-bonded (Hydrophobic) interactions;
#Amino acid residues involved in both interactions.

3.4 Docking interactions

The binding affinities among ACE and best two phytochemical compounds (Quercetin and Luteolin) that exhibited higher docking affinities in comparison with Captopril, a Sulfhydryl-containing agent were shown in Figure.3a-c. The docking interactions revealing the formation of H-bond interactions and Non-bonded (van-der Waal's) interactions between the nine phytochemical compounds and ACE binding site residues were explored in Table 2. It is observed that the interaction of standard drug Captopril is favoured by the formation of H-bonds with Gln281, Glu411, Lys511, His513, Tyr520 and Tyr523 while hydrophobic interactions with His353, His383, His513, Tyr520 and Tyr523. Interestingly, it is observed that the amino acids Histidine (His353, His383, and His513) and Tyrosine (Tyr523) in the binding site of ACE protein are crucial in favouring the interactions with all the nine compounds, which exhibited better dock score than that of captopril. It is noteworthy to mention that the compounds such as Quercetin (-33.0149 kJ/mol), Luteolin (-30.8914 kJ/mol), Isovitexin (-30.0155 kJ/mol) and Rutin (-29.4384 kJ/mol) exhibited significantly better binding affinities than the standard drug captropril. Interestingly, the interaction of these four comounds suggests are favoured by formation of vander Waals interaction with Phenyl alanine (Phe 457 and 527), which possibly that the Pheny alanine in the active site of ACE protein plays a crucial role for their better binding affinities.

The docking interactions along with their docking scores of three compounds that exhibited higher docking affinities in comparison with Lisinopril, a dicarboxylate-containing agent were shown in Figure.4a-c. The docking interactions revealing the formation of H-bond interactions and Non-bonded (van-der Waal's) interactions between these three phytochemical compounds along with standard drug Lisinopril and ACE binding site residues were explored in Table 3. It is observed that the interaction of standard drug Lisinopril is favoured by the formation of H-bonds with Gln281, His353, Ala354, His383, His387, Lys511, Tyr520 and Tyr523 and hydrophobic interactions with His353, Ser355, His383, His387, Glu411, Phe457, His513, Tyr520 and Tyr523. Similarly, it is observed that the amino acids Glutamine (Gln281), Histidine (His353), Lysine (Lys511) and Tyrosine (Tyr523) plays a crucial role in favouring the

interactions with all the three compounds including Lisinopril. Interestingly it is observed that the docking score of Rosemarinic acid (-34.6473 kJ/mol) is relatively better that that of Standard drug Lisinopril dock score (-33.8026 kJ/mol), While the dock score of Caffeic acid (-33.9872 kJ/mol) is also found to be slightly better than standard. It is observed the Rosemarinic acid interactions are supported by an additional amino acid Phenylalanine (Phe527) in the formation of nonbonded interactions while compared to other compound interactions. Thus it possibly suggests that the Pheny alanine in the active site of ACE protein plays a crucial role for its better binding affinities.

Thus the docking studies implies that the conserved amino acids such as Histidine (H) and Tyrosine (Y) in the binding pockets of ACE are vital in posing the better binding interaction with the phytocompounds than that of Sulfhydryl-containing ACE therapeutic, Captopril. Whereas the amino acids such as Glutamine (Q) and Valine (V) are significant in favouring the better interaction with phytocompounds than that Lisinopril, a dicarboxylate-containing agent. These docking interactions also envisages that the =O (keto group) present in the compounds and -NH (amino group) on the amino acids favors the H-bond interactions. Hence these findings clearly picturizes that the Rosemarinic acid could significantly possess better ACE inhibition activity and could be an alternative therapeutic agent to replace the drugs with severe side effects.

3.5 Pharmacophore Modeling and Validation

The pharmacophore model is generated by using the pharmacophore module of Discovery Studio. The Pharmacophore hypothesis generation is achieved by using auto pharmacophore generation option in Discovery Studio which considers the chemical feature types such as the hydrogen bond acceptor (HB_ACCEPTOR), hydrogen bond donor (HB_DONOR), hydrophobic feature (HYDROPHOBIC), negative ionizable feature (NEG_IONIZABLE), positive ionizable feature (POS_IONIZABLE) and aromatic ring (RING_AROMATIC) for the selected ligand.

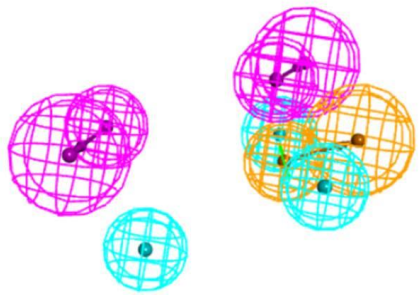


Figure.5: Generated Pharmacophore based on the Rosemarinic acid, Hydrogen bond donor (magenta) Hydrophobic (cyan) ; Ring aromatic (orange)

The ten pharmacophore models are generated by using Common Feature Pharmacophore Model Generation protocol in Discovery studio. For a statistically significant pharmacophore model, correlation coefficient and root mean square deviation (RMSD) are calculated. The best pharmacophore model was selected based on the high correlation coefficient and lower RMSD . The generated pharmacophoric features based on the Rosemarinic acid is shown in figure.5.

3.6 3D Database Screening

Search 3D Database protocol with best search option implemented in DS is used for database screening against Maybridge database consisting of more than one lakh compounds. The obtained database hits is screened using various filters such as estimated activity, Lipinski's rule of five, and ADMET properties. The final hit compounds after filtering are known as hit list and ranked according to the fit value, which is the degree of consistency with the pharmacophore model. To decrease the number of hits, a minimum fit value of >3, which is the lowest limit to qualify as a hit compound, is applied.

This lower limit of fit value is chosen according to the fit value obtained from the active molecule. The molecules with good fit scores are selected for further docking studies. The generated 3D pharmacophore of rosmeric acid is subjected to screen the compounds with the significant chemical features against May bridged database, exhibited 9 potential compounds that matches the generated pharmacophore (Table.4). These Hits are defined as those compounds that possess chemical functionalities that spatially overlap with corresponding features within the pharmacophoric model. The hits were subsequently fitted against the pharmacophore and assessed by Fit Value (Figure.6).

Table 4 The compounds matching pharmacophore and their fit values (Rosemeric acid)

S.No.	Maybridge compound	Fit Value
1.	PD 00533	2.66957
2.	CD 01374	1.86604
3.	CD 04888	1.74073
4.	CD 01278	1.17254
5.	BTB 04932	1.14923
6.	SPB 00952	0.866112
7.	RJC 03634	0.840245
8.	RJC 03429	0.36152
9.	RDR 01978	0.152094

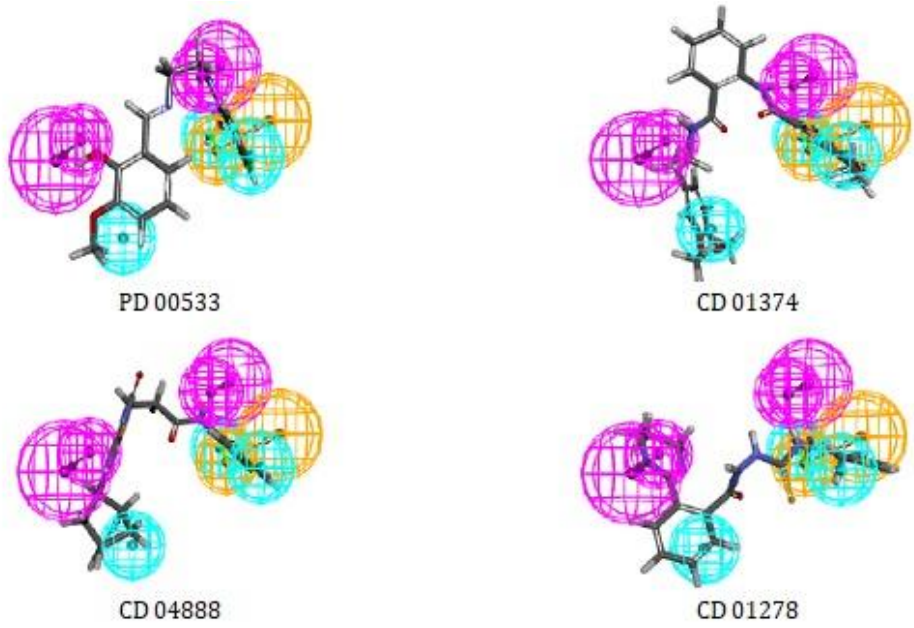


Figure.6 : The top four compounds matching the Pharmacophore

3.7 Molecular Docking

The Top 4 obtained compounds PD 00533, CD 01374, CD 04888 and CD 01278 were docked with in the active site of ACE2, and their docking interactions with their binding energies along with their pharmacophoric fit values were tabulated (Table.5). Among the obtained 4 hits from maybridge database, the compound PD 00533 exhibited the highest docking score of -38.4372 kJ/mol. The docking studies implies that the amino acids Alanine (Ala356), Histidine (His 513 and 353) and Water molecule (Hoh 2317) in the binding pockets of ACE are vital in posing the better binding interaction with the maybridge screened compound (PD 00533). While the non bonded interactions are favoured by Valine (Val518), Serine (Ser355), Histidine (His 353,387,383 and 513). These docking interactions also envisages that the =O (keto group) present in the compounds and NH (amino group) on the amino acids favors the Hbond interactions.

Table.5: Maybridge compounds with the fit values and docking scores

Compound	Fit value	Docking score
PD 00533	4.66957	-38. 4372
CD 01374	3.86604	-34.5687
CD 04888	2.56234	-32.5624
CD 01278	2.54782	-30.4587
BTB 04932	1.89542	-28.25687

Thus the pharmacophoric design and 3D database search along with the docking studies revealed that the May Bridge compound PD00533 having the better binding energy of -38.4372 kJ/mol might have a better inhibition activity against the ACE2 receptor.

3.8 Natural bond Analysis (HOMO-LUMO)

The Eigen value of LUMO–HOMO energy gap reflects the chemical activity of the molecule. The HOMO-LUMO Plot of PD00533 is shown in figure.8.

The HOMO–LUMO energy gap for PD 00533calculated at DFT level:

HOMO Energy = -6.8077 eV
LUMO Energy = -3.9086 eV
HOMO – LUMO energy gap = 2.90 eV

The Eigen value of LUMO–HOMO energy gap reflects the chemical activity of the molecule. The decrease in the HOMO and LUMO energy gap explains the eventual charge transfer interactions that are taking place within the molecule which might be due to the strong electron-accepting ability of the electron-acceptor groups. It is observed that the HOMOs have an overall π bonding character along with a considerable non-bonding character and LUMOs have an anti-bonding π* character. The strong charge transfer interaction is responsible for the bioactivity of the molecule. Thus it is observed that two compounds namely Rosemarinic acid and Caffeic acid showed relatively good binding affinity that the standard ACE inhibitor Lisinopril. Lisinopril.

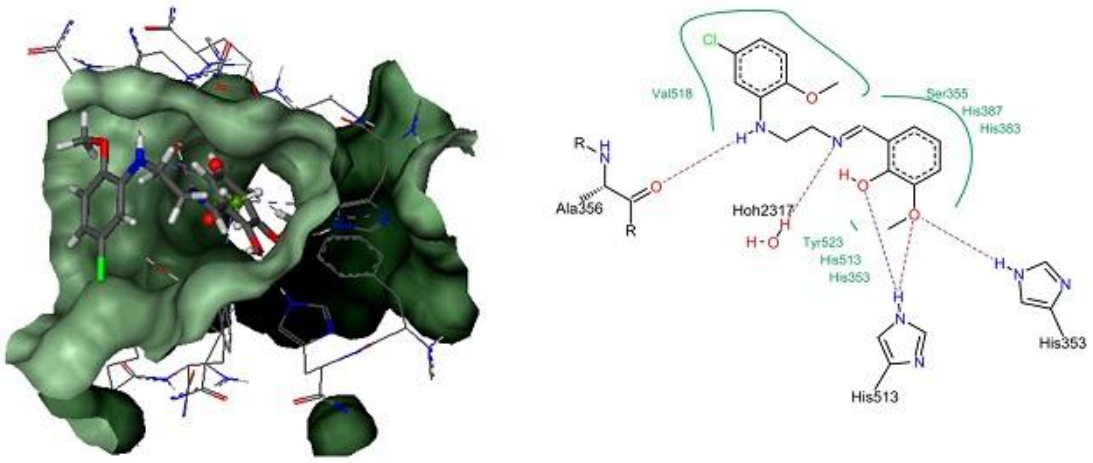


Figure.7: Docking complex and interactions of PD 00533 (-38.4372 kJ/mol)

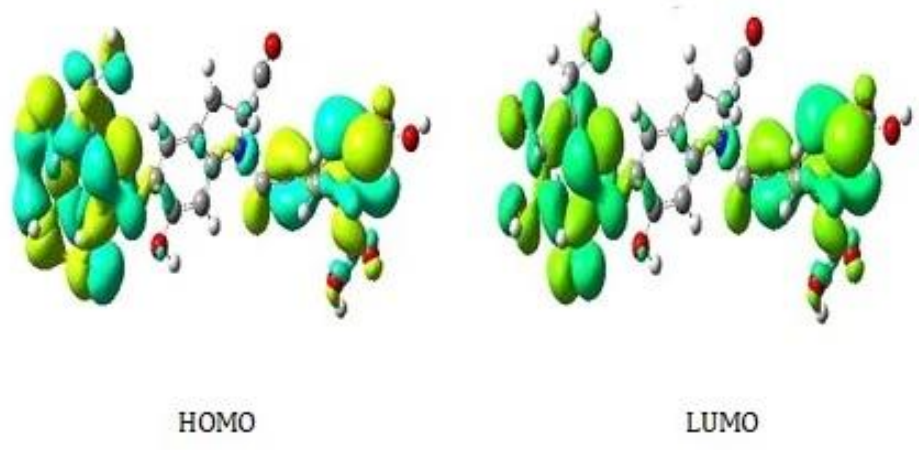


Figure 8 : The HOMO-LUMO plot for PD 00533 (compound obtained from Rosemmeric pharmacophore)

The compound PD 00533 also favors the necessary hydrogen bond interactions with in the activity site of ACE and thus identified as novel leads with anti-hypertensive activity. The HOMO–LUMO energy gap has a substantial influence on the calculated value that is found to be 2.90 eV. The lowering of HOMO–LUMO energy gap, a quantum–chemical descriptor, explains the charge transfer interactions taking place within the molecule through strong N–H···N and N–H···O hydrogen bonding which strengthens that compound PD00533 is bioactive and pharmaceutical in nature and thus suggested as novel leads with anti-hypertensive activity.

CONCLUSION:

Hypertension is a highly prevalent cardiovascular risk factor. Angiotensin Converting Enzyme (ACE), a metallo-peptidase is the best known important drug target in the treatment of hypertension and responds to broad range ACE inhibitors such as Captopril. In this study, 18 phytochemical compounds were screened for their anti-hypertensive activity against the x-ray crystal structure of human ACE in complex with lisinopril. It is observed that Rosemarinic acid showed relatively good binding affinity that the standard ACE inhibitor Lisinopril. Further, the 3D pharmacophore generated on Rosemarinic acid was screened against May bridged database and found that PD 00533 as novel leads with anti-hypertensive activity.

The hydrogen bonds network of PD 00533 has been thoroughly analyzed using NBO analysis and the molecular hydrogen bonding and charge transfer interaction present in the molecule emphasized the charge transfer interactions taking place within the molecule through strong N–H···N and N–H···O hydrogen bonding is crucial for its bioactivity. Further it implies that the NH group and =O present in the compounds favors the hbond interactions. The findings from these studies pave a path for the design of novel ACE inhibitors and also envisage that the amino acids Aspartic acid, Phenylalanine, Leucine and Glycine should be considered during its design for implying its action as a best ACE inhinitor compound against the potential target of angiotensin-converting enzyme.

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