



Ideal Drug for Blood Pressure

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ABSTRACT

Blood pressure, sometimes referred to as arterial blood pressure, is the pressure exerted by circulating blood upon the walls of blood vessels. Angiotensin is a peptide hormone that causes vasoconstriction followed by increase in blood pressure. Angiotensin I is converted to angiotensin II by the enzyme angiotensin-converting enzyme (ACE). ACE is a target for inactivation by ACE inhibitor drugs. ACE inhibitors are major anti-hypertensive drugs. Here, the ACE is disease causing receptor and the ACE inhibitors used as ligand. In the present investigation, most suitable ACE inhibitor was identified from frequently prescribed drugs such as perindopril, captopril, enalapril, lisinopril, ramipril, benazepril, fosinopril, trandolapril, moexipril and telmisartan through molecular docking. Based on the precision rate of docking and e-values, Trandolapril, Ramipril and Benazepril were identified as effective drug molecules. From the present investigation it is suggested that Trandolapril, Ramipril and Benazepril drug molecules could be used for regulating the blood pressure (Hypertension). Among the three, Trandolapril is the most effective drug molecule for controlling the hypertension.

Keywords: Angiotensin-converting enzyme (ACE), ACE inhibitor and molecular docking, Blood pressure.

INTRODUCTION

Blood pressure is the pressure exerted by circulating blood upon the walls of blood vessels, and is one of the principal vital signs. During each heartbeat, blood pressure varies between a maximum (systolic) and a minimum (diastolic) pressure.¹

Angiotensin is a powerful oligopeptide hormone that causes vasoconstriction followed by increase in blood pressure. It is derived from the precursor molecule angiotensinogen, a serum globulin produced in the liver.² Angiotensin I is formed by the action of renin on angiotensinogen. Angiotensin I appear to have no biological activity and exist solely as a precursor to angiotensin II. Angiotensin I is converted to angiotensin II by the enzyme angiotensin-converting enzyme (ACE). Angiotensin II increases blood pressure. Angiotensin II is degraded to angiotensin III. Angiotensin III is formed as a result of a cleavage at the N-terminus of Angiotensin II. Angiotensin IV is a hexapeptide that, like angiotensin III, also has some lesser activity.³

ACE is a target for inactivation by ACE inhibitor drugs. ACE inhibitors are major anti-hypertensive drugs. It can be divided into three groups based on their molecular structure. They are 1) Sulfhydryl-containing Captopril and Zofenopril, 2) Dicarboxylate-containing Enalapril, Ramipril, Quinapril, Perindopril, Lisinopril, Benazepril, Imdapril, Zofenopril and Trandolapril, and 3) Phosphonate-containing Fosinopril.^{4,5} All ACE inhibitors have similar antihypertensive efficacy when equivalent doses are administered. Patients with heart failure may

benefit from the combination in terms of reducing morbidity.⁶

In molecular docking, the protein (ACE receptor) can be thought of as the "lock" and the ligand (ACE inhibitors) can be thought of as a "key".⁷ The design and preparation of new potent ACE inhibitors still remains one of the main challenges in the intersection of the fields of chemistry, pharmacology and medicine.⁸ The present investigation aims to identify the most suitable ACE inhibitory drug molecules through bioinformatics tools and softwares.

MATERIALS AND METHODS

Literature pertaining to Angiotensin I & II, ACE protein and ACE inhibitors such as Benazepril, Captopril, Enalapril, Lisinopril, Ramipril, Fosinopril, Perindopril, Trandolapril, Moexipril and Telmisartan were retrieved from database, PubMed (www.ncbi.nlm.nih.gov/pubmed). Structure of ACE protein was retrieved from PDB databases (www.rcsb.org/). The molecular structures of drugs were retrieved from Chemspider database (www.chemspider.com/). Rasmol tool was used for molecular visualization (www.rasmol.org/). Swiss Pdb Viewer (www.swissmodel.expasy.org/) was used for the conversion of 2D structure into 3D chemical structure. The docking tool Hex was used for molecular docking (www.hex.loria.fr/). Binding sites, precision rate, 3-D structure of the ACE protein molecule and amino acid residues lining the active binding site were drawn through Q-site finder (www.modelling.leeds.ac.uk/qsitefinder/).

RESULTS AND DISCUSSION

Angiotensin

Angiotensin is a peptide hormone that causes the increase in blood pressure.² Angiotensinogen, a 12 amino acid peptide, is a precursor of Angiotensin I. This Angiotensin I is formed by the action of renin. Renin is produced in the kidneys, which cleaves the peptide bond between the leucine (Leu) and valine (Val) residues on angiotensinogen, creating the 10 amino acid peptide angiotensin I. Angiotensin I appears to have no biological activity and exists solely as a precursor to angiotensin II.³ Angiotensin I is converted to angiotensin II a 8 amino acid peptide through removal of two C-terminal residues by the enzyme angiotensin-converting enzyme (ACE).

Flow Chart Showing Conversion of Angiotensins I-IV After Stepwise Cleavage

Sequence of angiotensinogen (12aa) Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-...

↓

Sequence of angiotensin I (10 aa) Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu | Val-Ile-...

↓

Sequence of angiotensin II (8aa) Asp-Arg-Val-Tyr-Ile-His-Pro-Phe | His-Leu

↓

Sequence of angiotensin III (7 aa) Asp | Arg-Val-Tyr-Ile-His-Pro-Phe

↓

Sequence of angiotensin IV (6aa) Arg | Val-Tyr-Ile-His-Pro-Phe

Angiotensin-converting enzyme (ACE)

Angiotensin-converting enzyme (ACE) is a metalloprotease enzyme [9]. It is a kind of polymer protein containing 589 amino acid residues. Its molecular weight is 69725.40 (Figure 1). It has two primary functions: ACE catalyses the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor in the blood vascular system.¹⁰

Binding sites of ACE

In biology, the active site is the small portion of an enzyme where substrate molecules bind and undergo a chemical reaction.¹¹ The active site is usually found in a 3-D groove or pocket of the enzyme, lined with amino acid residues. These residues are involved in recognition of the ligands (drugs). Usually, an enzyme molecule has 10 possible ligand binding sites, out of which only one functions as active site, and the active site fits with one specific type of ligand molecule.¹² A tighter fit between an active site and the ligand molecule is believed to increase the efficiency of a reaction.¹³ In this investigation, 10th binding site is considered as the best active site involved

in the binding of ligands with the receptor molecule (Figure 2). In the present investigation, 10th binding site of ACE receptor molecules is the target binding site for the ligands (drugs).

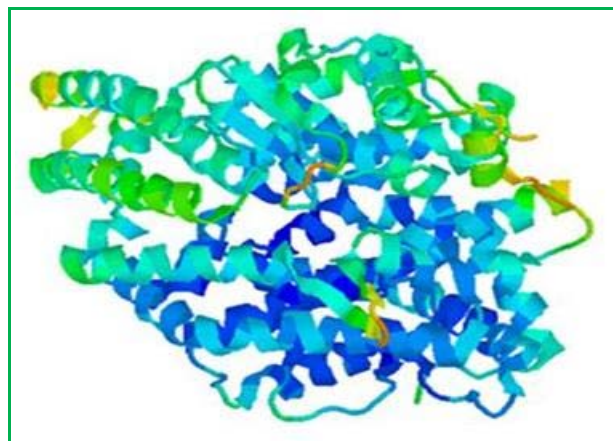


Figure 1: 3D structure of Angiotensin Converting Enzyme (ACE)

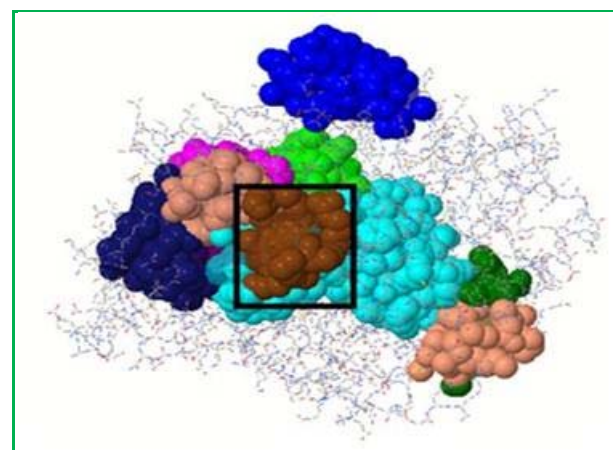


Figure 2: Ligand binding sites of ACE receptor showing the active site no.10

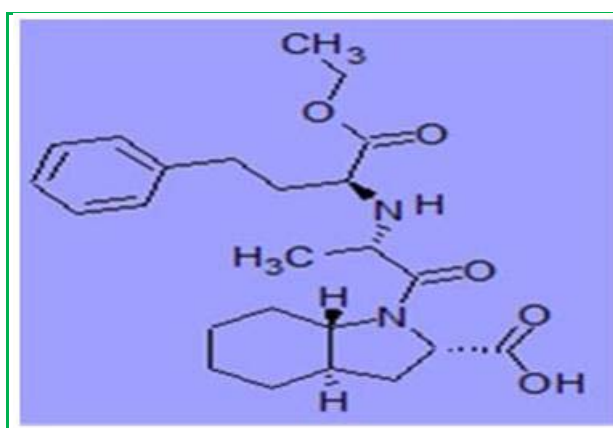


Figure 3: Molecular structure of Trandolapril

ACE inhibitors

ACE inhibition is the goal in the treatment of conditions such as high blood pressure, heart failure, diabetic nephropathy, and type 2 diabetes mellitus. Frequently prescribed ACE inhibitors include perindopril, captopril, enalapril, lisinopril, and ramipril, benazepril, fosinopril,

trandolapril, moexipril and telmisartan. ACE inhibitors block the conversion of angiotensin I to angiotensin II.¹⁴ According to¹⁵, evening/bedtime ingestion of the angiotensin-converting enzyme inhibitors (ACEIs) benazepril, captopril, enalapril, lisinopril, perindopril, quinapril, ramipril, spirapril, trandolapril, and zofenopril exerts more marked effect on the asleep than awake systolic (SBP) and diastolic (DBP) blood pressure. Benazepril is a medication used to treat high blood pressure, congestive heart failure, and chronic renal failure.¹⁶ Concluded that amlodipine and benazepril in single-pill combinations is more effective than the amlodipine alone for rapid BP control in patients with severe hypertension. Effects of combined benazepril/hydrochlorothiazide were more effective than amlodipine combined with benazepril.¹⁷

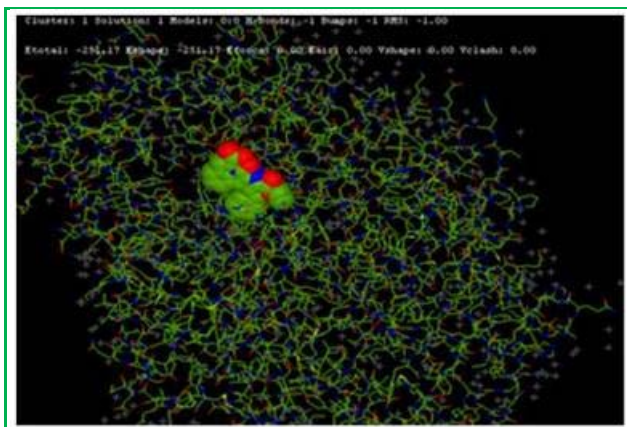


Figure 4: Molecular docking of ACE receptor with Trandolapril ligand

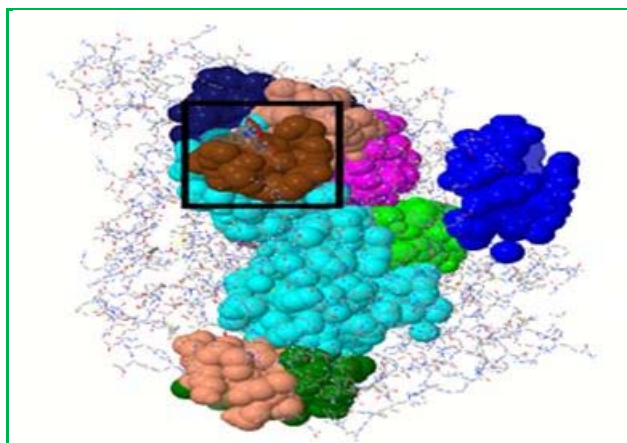


Figure 5: Binding of Benazepril, Ramipril and Trandolapril drugs with the common active 10th site of ACE receptor (Note the binding of the smaller drug molecule on the receptor active site no.10)

Enalapril is an angiotensin converting enzyme (ACE) inhibitor used in the treatment of hypertension and some types of chronic heart failure. One of the actions of angiotensin II is the vasoconstriction of blood vessels resulting in an increase in blood pressure. ACE inhibitors such as enalapril prevent this effect. Enalapril has been shown to lower the death rate in systolic heart failure. Enalapril was the first member of the group known as the

dicarboxylate-containing ACE inhibitors.¹⁸ Captopril was the first ACE inhibitor developed and was considered as a breakthrough both because of its novel mechanism of action and also because of the revolutionary development process.¹⁹

Lisinopril has a long half-life and tissue penetration, and is not metabolized by the liver. It is a well tolerated standard medication in treating hypertension; heart failure and diabetic nephropathy.²⁰ Serious side effects such as angio-oedema are very rare.²¹ Lisinopril significantly reduced mean arterial blood pressure, and attenuated proteinuria level in patients subjected to this study in lisinopril 10mg dose dependent manner. In conclusion, lisinopril is of beneficial of renoprotection and in lowering BP.²²

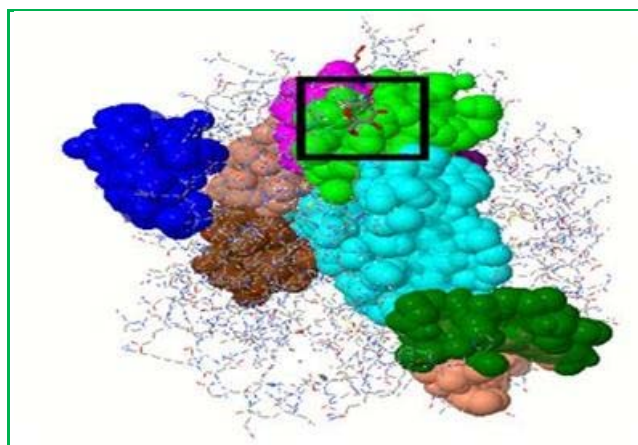


Figure 6: Binding of Lisinopril, Fosinopril, Moexipril and Telmisartan drugs with the common active 1st site of ACE receptor (Note the binding of the smaller drug molecule on the receptor active site no.1)

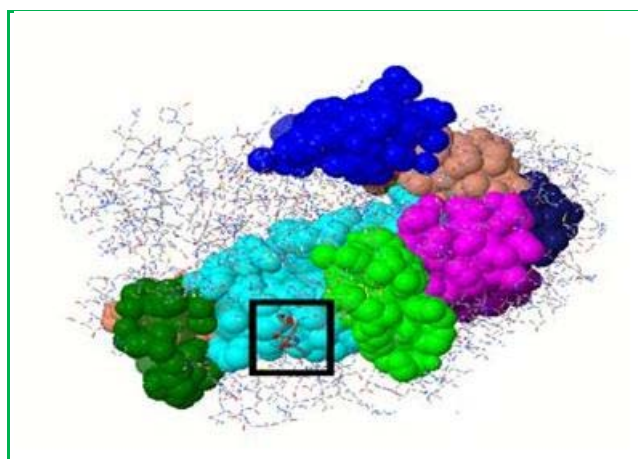


Figure 7: Binding of Captopril drug with the active site-2 of ACE receptor (Note the binding of the smaller drug molecule on the receptor active site no.2)

Ramipril is an angiotensin-converting enzyme (ACE) inhibitor, used to treat high blood pressure, heart failure, heart attack, stroke and cardiovascular diseases.¹⁴ Fosinopril is the only phosphinate-containing ACE inhibitor.²³ investigated the hemodynamic and clinical effects of fosinopril in patients with heart failure.²⁴

studied and concluded that administration of fosinopril at 20 and 40 mg was safe and well tolerated.

Perindopril is a long-acting ACE inhibitor. The study indicates that perindopril is superior to enalapril in producing monocyte-suppressing and systemic anti-inflammatory effects in normal hypertensive patients with coronary artery disease.²⁵ In recent decades, the most successful strategy for controlling blood pressure has been inhibition of the angiotensin-converting enzyme (ACE).

Trandolapril (Figure 3) acts by competitive inhibition of Angiotensin Converting Enzyme (ACE), a key enzyme in the renin-angiotensin system which plays an important role in regulating blood pressure. Trandolapril demonstrated a favourable safety and effectiveness profile.²⁶

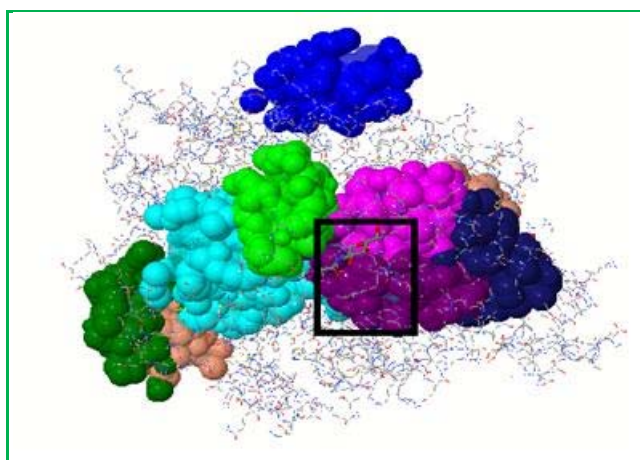


Figure 8: Binding of Enalapril and Perindopril drugs with the common active 5th site of ACE receptor (Note the binding of the smaller drug molecule on the receptor active site no.5)

Table 1: Molecular docking results between the ACE and the drug molecules

ACE inhibiting Drugs (Ligand)	e-values	Predicted ligand binding site	Precision rate in %
Benazepril	-253.31	Predicted site 10	92.7
Captopril	-161.04	Predicted site 2	50
Enalapril	-249.85	Predicted site 5	44
Lisinopril	-280.00	Predicted site 1	16.5
Ramipril	-243.15	Predicted site 10	87.8
Fosinopril	-298.93	Predicted site 1	10.5
Perindopril	-241.43	Predicted site 5	34.7
Trandolapril	-251.17	Predicted site 10	95.1
Moexipril	-267.36	Predicted site 1	13.6
Telmisartan	-267.66	Predicted site 1	10.5

Moexipril hydrochloride is a potent orally active non-sulphydryl angiotensin converting enzyme inhibitor (ACE) which is used for the treatment of hypertension and congestive heart failure. Moexipril can be administered alone or together with other antihypertensives or

diuretics. It works by inhibiting the conversion of angiotensin I to angiotensin II.²⁷

Telmisartan is an angiotensin II receptor antagonist used in the management of hypertension. Telmisartan is indicated for the prevention of cardiovascular events in high-risk patients, based on comparable efficacy to the angiotensin-converting enzyme (ACE) inhibitors, ramipril, enalapril and lisinopril in the on going telmisartan alone and in combination with ramipril. Telmisartan and ACE inhibitors produced comparable blood pressure reductions at marked doses. Telmisartan and ACE inhibitors are suitable for the prevention of cardiovascular events in high-risk patients, but telmisartan is better tolerated.²⁸ People affected by hypertension are using the physician directed synthetic drug molecules such as Benazepril, Captopril, Enalapril, Lisinopril, Ramipril, Fosinopril, Perindopril, Trandolapril, Telmisartan and Moexipril, in spite of the various ACE inhibitors available.

Molecular docking

Docking plays a significant role in the prediction of the binding orientation, affinity, and activity of small drug molecule candidates to their protein targets with known 3D structures. Hence docking serves as an important tool in the rational computer-assisted drug design.²⁹ In the present study, in order to understand the potential drug molecule for controlling the blood pressure, molecular docking study was carried out using various drug molecules commonly prescribed by the physicians. These drug molecules, ACE inhibitors, acted as ligand molecules and the ACE as the receptor molecule. Hex software was used to conduct the molecular docking. In the docking, the e-values obtained for the various drug molecules were ranging from -161.04 to -298.93 (Table 1). In this docking, the binding site and the success (precision) rate of the docking were also calculated. From the result, the precision rate was more than 85% in drug molecules like Trandolapril, Benazepril and Ramipril and all of them docked at the 10th ligand binding site of ACE receptor molecule. Among them Trandolapril showed 95.1% precision in docking and used the minimum energy value of -251.17 (Figure 4). In the ligand binding site of the angiotensin converting enzyme, ASP, ARG, SER, TYR, GLU, THR, PRO, SER, LEU and GLU amino acid residues were involved in the molecular interaction between the binding site of the ACE and ligand molecules.

In ACE receptor molecule, 10 ligand binding sites were located. During molecular docking, the other effective ligand molecules such as Benazepril and Ramipril showed effective binding with 10th binding site. Benazepril and Ramipril showed 92.7% and 87.8% precision rate of molecular docking respectively. Both the ligands, Benazepril and Ramipril also interacted with the amino acids of the 10th binding site such as ASP, ARG, SER, TYR, GLU, THR, PRO, SER, LEU and GLU. Both the ligands, Benazepril and Ramipril showed the energy value of the docking as -253.31 and -243.15 respectively (Table 1).

Among the above three ligands which showed effective binding with the 10th binding site (Figure 5), Trandolapril showing 95.1% precision rate and e-value of -251.17 was considered as most effective drug molecule to control the blood pressure. The other two ligands Benazepril and Ramipril also may be considered as effective drugs since they bind with 10th binding site showing precision rate as 92.7% and 87.8% respectively (Table 1).

Drug molecules such as Lisinopril, Fosinopril, Moexipril and Telmisartan showed a poor binding with the active sites of the receptor ACE. Out of ten sites available all the four drug molecules showed the binding with the site no.1 and the precision rate was less than 16.5%. Lisinopril, Fosinopril, Moexipril and Telmisartan showed e-values of the binding as -280.00, -298.93, -267.36 and -267.66 respectively (Table 1; Figure 6). The ligand Captopril showed binding with site 2 of ACE showing 50% precision. The e-value obtained in the docking was -161.04 which is very less than that of the other ligands (Table 1; Figure 7). The remaining two drug ligand molecules Enalapril and Perindopril showed binding with site-5 of the ACE receptor molecule. The docking energy value of the ACE with Enalapril and Perindopril was -249.85 and -241.43 respectively. The precision rate of binding was very less with only 44% and 34.7% respectively (Table 1; Figure 8).

CONCLUSION

The receptor-ligand interactions play a significant role in molecular docking and drug designing. In the present investigation, the receptor of human ACE interacted with 10 ACE inhibitory drug molecules, out of which Benazepril, Ramipril and Trandolapril were selected. In ACE receptor molecule 10 ligand binding sites were located. In the 10th binding site, three ligands, Benazepril, Ramipril and Trandolapril interacted with the amino acids such as ASP, ARG, SER, TYR, GLU, THR, PRO, SER, LEU and GLU. Such ligands, Benazepril, Ramipril and Trandolapril which showed more than 85% of binding at the 10th ligand binding site, are considered to be more effective in lowering the blood pressure. Among the three, Trandolapril, which showed 95.1% precision rate, was the most effective drug molecule for controlling the blood pressure.

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