

Treatment and Management of Hypertension by Targeting ACE Inhibitors: *in silico* Approach

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Abstract: Hypertension means increase in blood pressure. There are different drugs which are available both as single dose and as combination therapy for treatment and management of hypertension. Our target is Angiotensin Converting Enzyme (ACE) inhibitors for better therapy or improved therapy of the hypertension patient. ACE in complex with inhibitor lisinopril, zinc cation and chloride ions (anions) have a similar structure to angiotensin I and bind to the active site of the ACE protein. The literature suggested that there are different classes of ACE inhibitors and describes their interaction with currently available drugs. We have also compiled the data on the proper management of hypertension with another relevant disease like diabetes. The number of available PDB three dimensional structure of ACE protein having different organism (74); *Homo sapiens* (49), *Drosophila melanogaster* (22), *Severe acute respiratory* (5), *Paguma larvata* (5), *Bacillus thermoproteolyticus* (3), *Severe acute respiratory* (3), *Gloydus blomhoffii* (2), *Other* (3). Our target is a well-known protein with high resolution in a human structure that is crystal structure of the Angiotensin-1 converting enzyme N-domain in complex with amyloid-beta 35-42 (PDB ID-5AMB) of recently submitted (2015) with high resolution (1.55 Å). The characteristic features of ACE having a zinc binding metallopeptidase consist of two domain of N and C terminal (different binding pattern). We have designed a better ligand interaction with this protein.

Keywords: Hypertension, ACE inhibitors, Angiotensin.

Introduction

Hypertension and diabetes type 2 (T2D) have elicited the need to investigate in more depth and extensiveness the risk factors that contribute for the treatment and management of these disease conditions in order to have a more comprehensive vision of the process to illuminate the path towards more precise and effective preventive interventions [1]. Usually and probably hypertension is a compensatory process, it proceeds with arteriosclerosis and chronic nephritis and in such cases operates as a cause rather than a symptom of these diseases [2, 3]. For the greater number of cases they make their appearance during the fifth decade of life [4]. There is

a correlation relation between hypertension and diabetic person (diet condition) [5]. All case of hypertension may be included in two general groups that are symptomatic group that includes in which primary condition is known (high blood pressure); a person can understand the result or symptoms of hypertension. Another essential hypertension group is having no definitely and discoverable cause in which a patient may be treated under observation for months [6]. A fairly complete laboratory study, X-ray and clinical study were made to diagnose the hypertension disease condition [7]. Treatment of hypertension has been studied most assiduously by Bright and his followers at Gay's hospital. A sphygmomanometer is familiar to us in the medical journals, so that it is reasonable to assume that the usefulness of such observation is being appreciated by our profession [8]. No doubt it is a bulky instrument, but it is equally true that there is no pocket substitute which can be trusted to read the degree of arterial tension with as great degree of accuracy. Single reading must not be trusted, to establish the existence of permanent hypertension, at least 3 or 4 observations should be made, if possible daily [9, 10].

Recent advancement of hypertension treatment

The cause of hypertension falls under two main categories, one is mechanical and the other is a chemical means [11]. Mechanical means argues that hypertension is due to an occlusive disease, such as endarteritis, which blocks partially or completely all the arteries of the body [8]. Some cases that have admitted with a normal or elevated pressure and during rest in bed the pressure and some have risen, during these variations the heart has not resumed its normal condition [8]. It should never fall to normal and certainly should not rise. Whereas, chemical means chemical agents that are soluble bodies which can permeate the whole vascular system, operating either on the ends of afferent nerves, on vasomotor center, or on the termination of motor nerve distributed to the muscular coats of blood vessels or to the muscular elements of heart. Interesting development have recently been made that pressor bodies elaborated in the intestine are eliminated in the kidney and diabetics person is ultimately lead to failure of kidney, the ethereal sulfates [12]. Such bodies are absorbed through intestinal mucosa and owing to faulty condition of kidney and met with hypertension case, accumulate in the system and lead to the hypertension [13].

Treatment and management of hypertension

It is necessary to warn that, even by the use of sphygmomanometer, no one can find out hypertension in every case in the disease of circulation, hypertension is indicated by intra arterial pressure [14]. Whereas at one time, it was considered as result of syphilis and arteriosclerosis, this is a natural result not cause. The reason for hypertension may be stated briefly to be an increase in the peripheral resistance in arterial circulation [15]. The exact cause of this condition is a mystery. This is the fact that there may be number of associated phenomenon such as obesity, hyperthyroidism and gout, but relationship of these is still to be explained [16]. Antihypertensive drugs may be used to treat the hypertension (high blood pressure) that may be caused due to any reason [17]. There are many classes of antihypertensive drugs which lower the blood pressure by different means. A diuretic includes thiazide, Loop Diuretics for example hydrochlorothiazide, furosemide, spironolactone, bumetanide. ACE Inhibitors includes captopril, enalapril, ramipril. AT_1 receptor blocker; Losartan, candesartan, Ca^{2+} channel blockers; verapamil, diltiazem, nifedipine, amlodipine; Vasodilators-Sodium nitroprusside, diazoxide; α -adrenergic blockers – terazosin, perazosin; β -blockers – atenolol, metoprolol, propranolol (Fig. 1).

Role of angiotensin-converting enzyme

The renin-angiotensin system (RAS) plays an important role in an interconnected set of a mechanism for the control of the volume, pressure, and electrolyte composition of blood salt homeostasis and may play a role in the pathogenesis of aspects of the metabolic syndrome [18]. Angiotensin converting enzymes (ACE) is a central component of the RAS, which regulated blood pressure by adapting the volume of fluids in the body [19]. The main function of ACE is to converts hormone angiotensin I into the angiotensin II (active vasoconstrictor). Therefore, ACE indirectly increases blood pressure by causing blood vessels to constrict. These enzymes are located mainly in capillaries of the lungs but can also be found in endothelial and kidney epithelial cells. ACE is also known as peptidase P, dipeptide hydrolase, angitensin-converting enzyme, hypertension converting enzyme, peptidyl- dipeptide hydrolase (PDH).

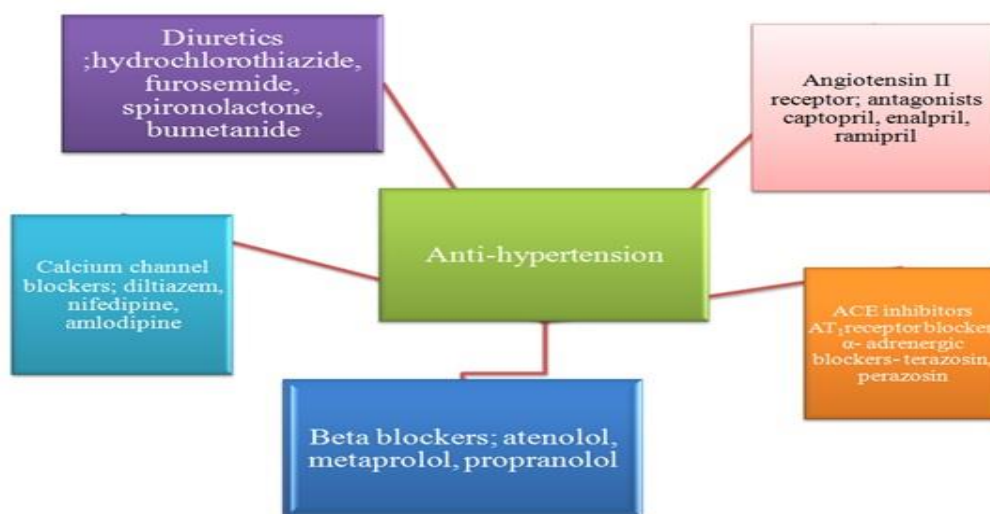


Fig. 1 Classification of anti-hypertensive inhibitors based on different classes of drugs

ACE inhibitors used in the treatment of hypertension

ACE in complex with inhibitor lisinopril, zinc cation and chloride ions (anions) has similar structure to angiotensin I and binds to the active site of ACE [20]. ACE inhibitors are widely used as pharmaceutical drugs in the treatment of condition such as high blood pressure, heart failure, diabetic nephropathy and type 2 diabetes mellitus [21]. That leads to decrease in formation of angiotensin II and decreased metabolism of bradykinin, which leads to systematic dilation of the arteries and veins and a decrease in arterial blood pressure [22]. Angiotensin-converting enzyme (ACE) inhibitors treat a variety of conditions, such as high blood pressure, scleroderma and migraines [6, 23]. Angiotensin II enzyme is a very potent chemical produced the body that primarily circulates in the blood. ACE inhibitor prevents an enzyme in your body that narrows your blood vessels and release hormones that can raise the blood pressure. This narrowing can cause high blood pressure and force heart to work harder [24].

ACE classification of inhibitors with details studies

Classification of ACE inhibitors can be divided into three groups based on their molecular structure: 1) sulfhydryl containing agents; Captopril (active drug), the first ACE inhibitor, Zofenopril, Alacepril and Moveltipril; 2) Dicarboxylate-containing agents includes the largest group, including: Enalapril, Ramipril, Quinapril, Perindopril, Lisinopril (active drug), Benazepril, Cilazapril and 3) Phosphonate-containing agents includes Fosinopril and SQ 29852 as shown in Fig. 2 [25]. ACE inhibitors are widely used to prevent, treat or improve the symptoms in conditions such as high blood pressure, coronary artery disease, heart failure,

diabetes, certain chronic kidney diseases, heart attacks, scleroderma and migraines. Chemical structure of ACE inhibitors and their used for the treatment of hypertension is depending upon condition of health and the condition being treated. People with chronic kidney disease may benefit from having an ACE inhibitor as a one of their medication [26].

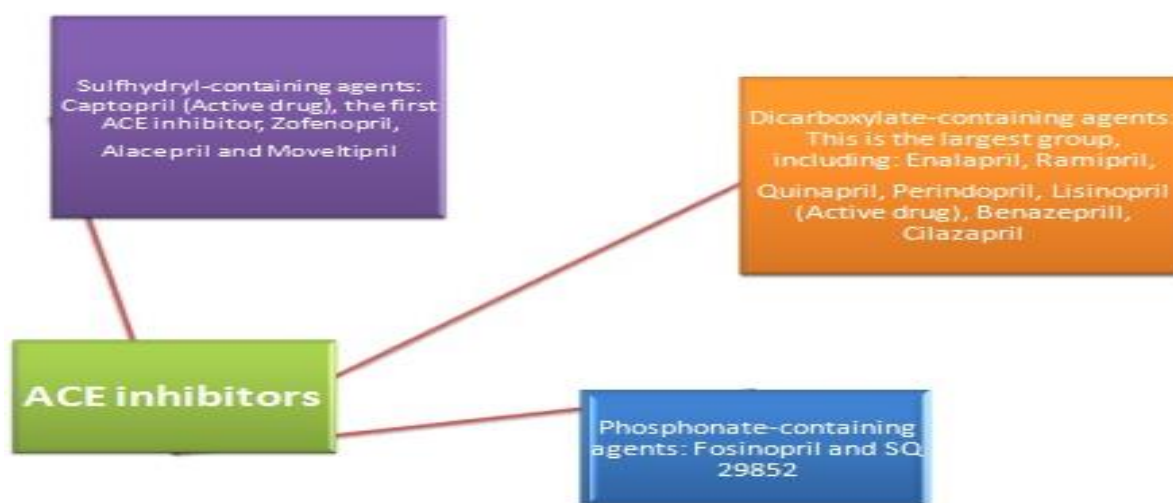


Fig. 2 Classification of ACE inhibitors based on their chemical groups that is sulpharyl group, phosphate group

Enalapril ($C_{20}H_{28}N_2O_5$): Enalapril, the first dicarboxylate containing ACE inhibitor. It is administered orally as the monoethyl enalapril, which serves as a prodrug [27]. Captopril ($C_9H_{15}NO_3S$): Captopril was the first inhibitor for clinical trial studies. According to Ondetti and colleagues has proposed a mechanism of angiotensin-converting enzyme of their inhibitors, captopril interacts with the enzyme through several bonds includes electrostatic, hydrogenic and lipophilic connections [28, 29]. Lisinopril ($C_{21}H_{31}N_3O_5$): Lisinopril (lye-SIN-o-pril) is simply the lysine analog of enalapril. Unlike enalapril, lisinopril itself is active with a long duration of action. Historically, lisinopril was the third ACE inhibitor, after captopril and enalapril, and was introduced into therapy in the early 1990s. Lisinopril has a number of properties that distinguish it from other ACE inhibitors: it is hydrophilic, has long half-life and tissue penetration and is not metabolized by the liver. Ramipril ($C_{23}H_{32}N_2O_5$): Ramipril is a prodrug and is converted to the active metabolite ramipril by liver esterase enzymes. Ramipril, unlike enalapril, possesses high lipophilic property that promotes penetration of ramipril in various tissues [30]. There are some anti-inflammatory activities due to inhibition of PGI₂ biosynthesis in the vascular tissue that inhibits adrenergic action in central nervous system and heart and also inhibits enkephalinase enzyme [31]. Benazepril ($C_{24}H_{28}N_2O_5$): Another non sulphydryl prodrug ACE inhibitor is useful in patients with mild to moderate hypertension. It is beneficial for patients with congestive heart failure and also decreased systemic and pulmonary resistance. They are useful in geriatric patients [32] and the structure is presented in Fig. 3.

Quinapril ($C_{25}H_{30}N_2O_5$) includes under a class of carboxylic acid inhibitor having tetrahydroisoquinoline analogue of endopril. It is a non-sulphydryl ACE inhibitor having the newer and second generation inhibitor. It is a prodrug and converts to the active metabolite quinapril [33]. Excessive hypotension is the most common reaction and dry hacking cough is another adverse effect. It is intermediate-acting ACE-I with a half-life shorter than of enalapril. Quinapril inhibits the contractile and pressor effects of angiotensin I in rabbit aorta [34]. Zofenopril ($C_{22}H_{23}NO_4S_2$) is also a prodrug that, once absorbed, undergoes rapid and complete hydrolysis to the sulphydryl-containing active metabolite that is called as zofenopril [35].

The ACE inhibitor effects of zofenopril, via Zofenopril, were found *in vitro* and *in vivo* to be 3 to 10 times higher on a molar basis than that of captopril [36].

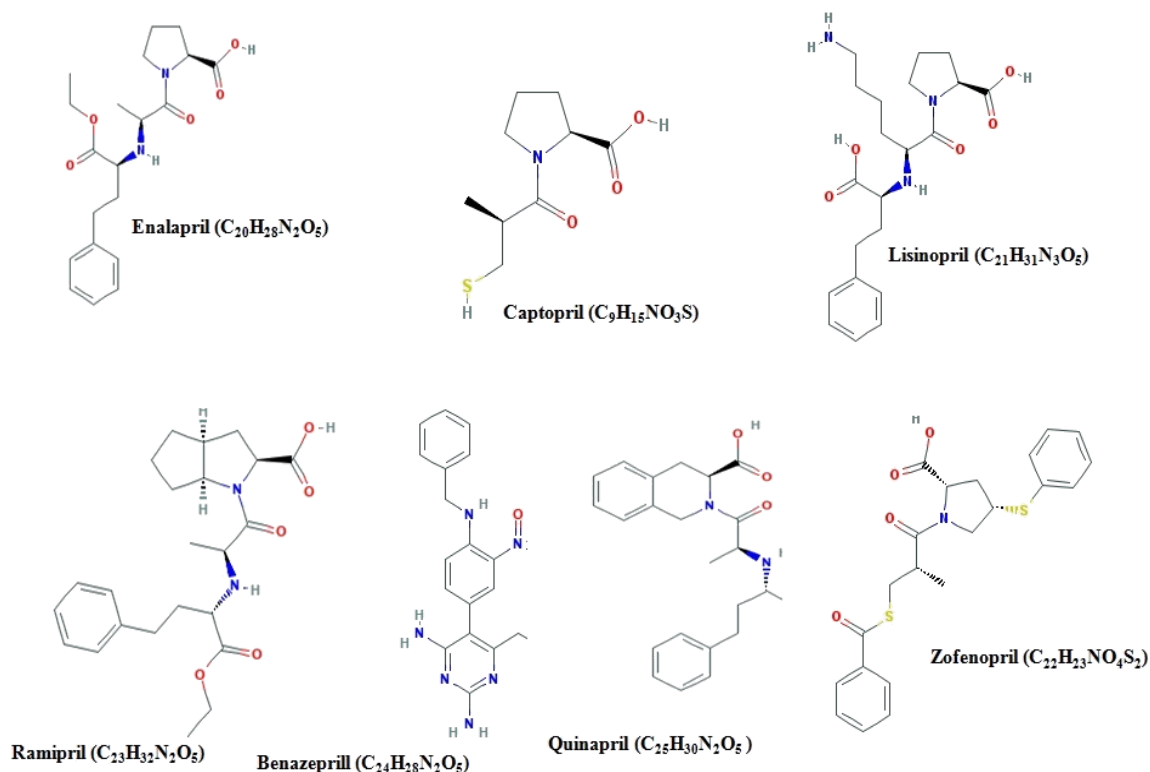


Fig. 3 Chemical structure of currently available drugs of ACE inhibitors

Zofenopril (or zofenoprilum) is also a class of ACE inhibitor having cardio protective properties that indicates for the treatment of high blood pressure. Mechanism of action of these drugs inhibits competitively with the activity of ACE to prevent formation of the active octapeptide from inactive decapeptide [37]. This occurs in blood and tissues including kidney, heart, blood vessels, adrenal gland and brain. But ACE inhibitors also lower blood pressure when there is normal or low activity of the renin-angiotensin system (Fig. 4) [38].

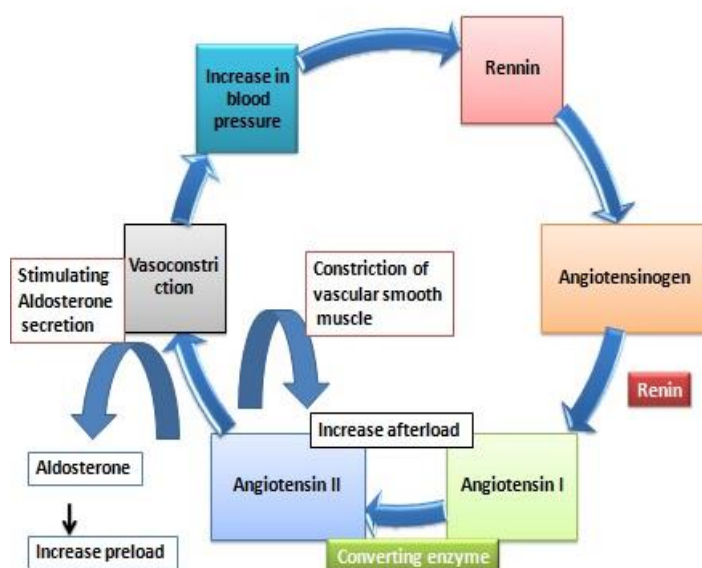


Fig. 4 Renin-angiotensin system for production of rennin that regulates the vasodilatation and contraction of blood vessels

Drug interactions for ACE inhibitors are common to all angiotensin-converting enzyme inhibitors include those with diuretic and other antihypertensive agents, in Table 1 included the interaction with other drugs.

Table 1. List of drugs, which interfere with other drugs (drug-drug interaction)

Drugs	ACE inhibitors	Probable mechanism	Result of interaction	References
Allopurinol	Captopril	Unknown	Increase risk of hypertension	[39, 40]
Antacids	All	-	Decrease bioavailability of ACE inhibitors	[41, 42]
COX-2 selective inhibitors	-	Interference with production of vasodilators	Decrease antihypertensive effect	[18, 43]
Digoxin	All	Deterioration of renal function	Either increase or decrease plasm dogixin level	[44]
Loop diuretics	All	Vasodilatation relative intravascular and volume depletion	Excessive reduction in B.P., effect of loop diuretic may be reduce	[45]
Iron salts	All	-	Reduction of Captopril level unless administration is serrated by at least two hours.	[46]
Potassium preparations or potassium-sparing diuretics	All	lower aldosterone level	Elevate serum potassium level	[47-49]
NSAIDs	All	Inhibitions of prostaglandin synthesis	Decreased hypertensive synthesis	[50]
Phenothiazides	All	Diminished response to pressor amines	Increased pharmacological level of ACE inhibitors	[51]
Rifampin	Captopril	-	Decreased pharmacological effect of Enalpril	[52, 53]
Tetracycline	Quinapril	-	Decreased absorption of tetracycline(may result from high magnesium content of quinapril tablets	[54, 55]

A side effect of these classes of drugs includes and doctors commonly prescribe ACE inhibitors because they do not often cause side effects [56]. Possible side effects includes, dry cough, increased blood-potassium level (hyperkalemia), fatigue, dizziness, headache, loss of taste.

In rare cases but more commonly in blacks and in smokers ACE inhibitors can cause some areas of your tissues to swell (angioedema). If it occurs in the throat region that often swelling can be life threatening condition. One of the drug-drug interactions between non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen sodium decreases the effectiveness of ACE inhibitors. Because ACE inhibitors can cause birth defects, one should always take ACE inhibitors after doctor's prescription especially if lady is pregnant or plan to get pregnant [57].

ACE protein structure and classification based on search into PDB server

There are a number of 3D structures of ACE proteins in PDB database [58] which is classified based on year, organism, and presence of ligand, experimental methods and other parameters. Selection of the 3D structure of ACE protein, which is based on three dimensional data, the recent experimental data of higher resolution was selected for further studies of selected 3D structure of ACE protein (PDB ID-5AMB). Advances in detection and identification of OP poisoning by selecting crystal structure of human acetylcholinesterase (AChE) were performed to find a better management and treatment of Acute organophosphorous pesticide (OP) [59]. The protein ligand interaction of complex protein of HGPRT [60-62], NDM1 [63], gBP21 protein [64] and LdGK protein [65] of molecular modeling approach were used to validate the results in this studies. *In vitro* studies of acetohydrazide analogues were performed against promastigotes for promises a better choice of drug [66]. Study of interaction of amyloid peptides ($A\beta$) with receptor for advanced glycation end products (RAGE) polymorphism and molecular dynamics study on RAGE- $A\beta$ 42 interaction [67]. The protein structure of ACE protein in PDB database in which total 1639 structure, unrelated structure (434), citations (789) and ligands (705) and percentage of these structures were found and suggested that the proteins of higher number is having structure as shown in Fig. 5A.

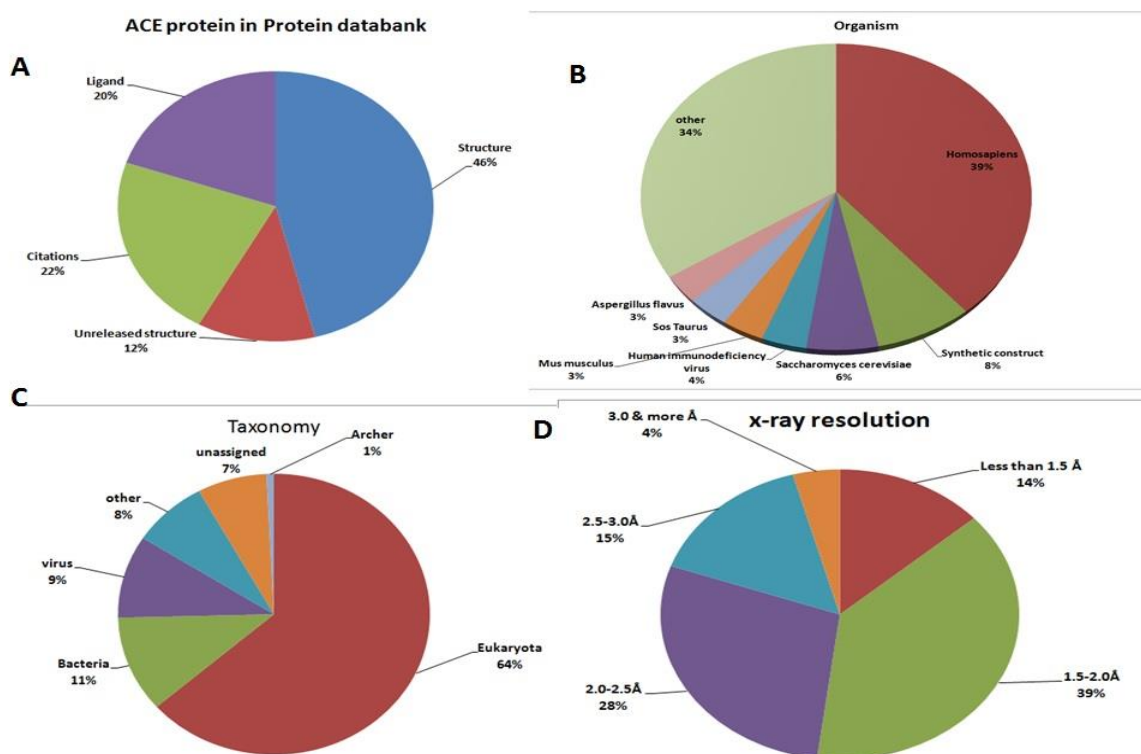


Fig. 5 The ACE protein in PDB database is shown based on:
A) Structure; B) Organism; C) Taxonomy and D) X-ray resolution.

Higher number of solved structure of ACE protein in protein database is *Homo sapience* (620), Synthetic construct (125), *Saccharomyces cerevisiae* (92), Human immunodeficiency virus (58), *Mus musculus* (54), *Sos Taurus* (53), *Aspergillus flavus* (49) and other (547) out of total structures in percentage (Fig. 5B). Based on the structures of their taxonomy the eukaryotes have maximum number of PDB structure (1161) of 64% followed by other bacteria, virus etc., as shown in Fig. 5C. Fig. 5D has shown the X-ray resolution of 1.5-2.0 range has higher number of structures (39%) of 549 number of structures. Polymer type based classification of ACE protein in which protein has 1608 structures whereas mixed type is 30 and DNA type only one (1). The uniprot molecule name of these proteins were having classification like caspase has 77, cyclin-dependent kinase 2; 62 as shown in Fig. 6.

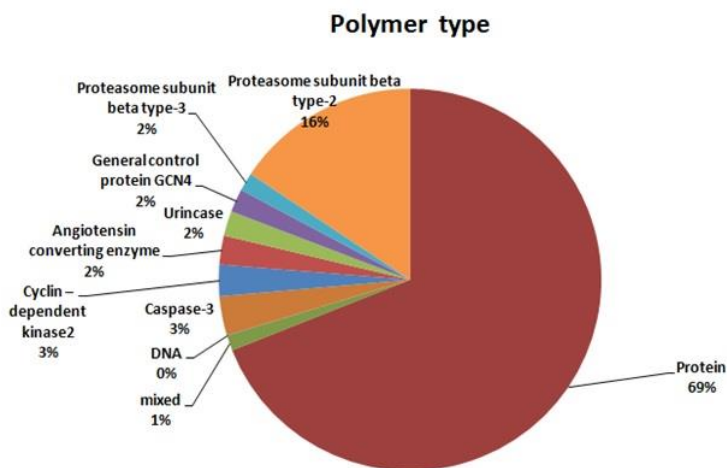


Fig. 6 Classification of ACE enzymes based on Polymer type that higher is protein (1608 structures) of 69%, mixed 30 and DNA type (1). The uniprot molecule name of these proteins were having classification like Caspase, cyclin-dependent kinase 2, etc.

The experimental method based on classification of solve structure of ACE protein that includes X-ray (1422), solution of NMR (192), electron microscopy (21), fiber diffraction (2), hybrid (2) as shown in Fig. 7.

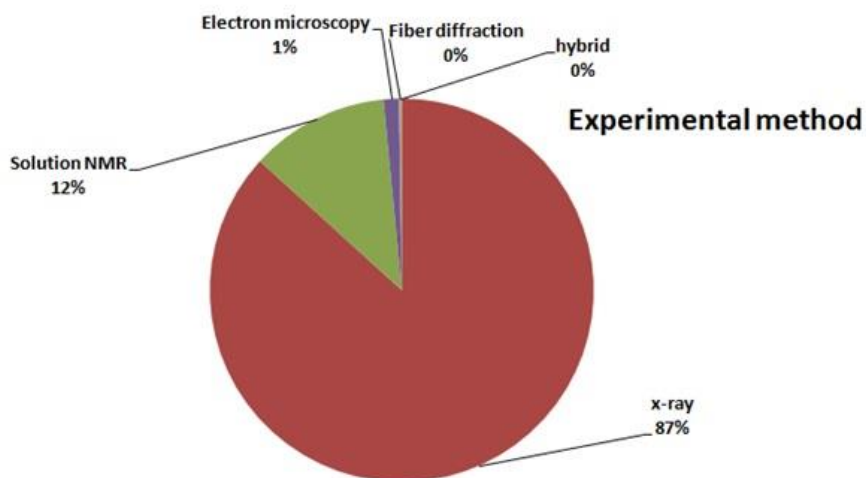


Fig. 7 The classification based on experimental method included X-ray (87%), solution of NMR (12%), electron microscopy (1%), fiber diffraction (0%), hybrid (0%)

The enzymatic based classification of ACE proteins in PDB database has shown the hydrolases (466), transferase (218), oxidoreductases (115), lyases (38), ligases (29) and isomerase (5) (Fig. 8).

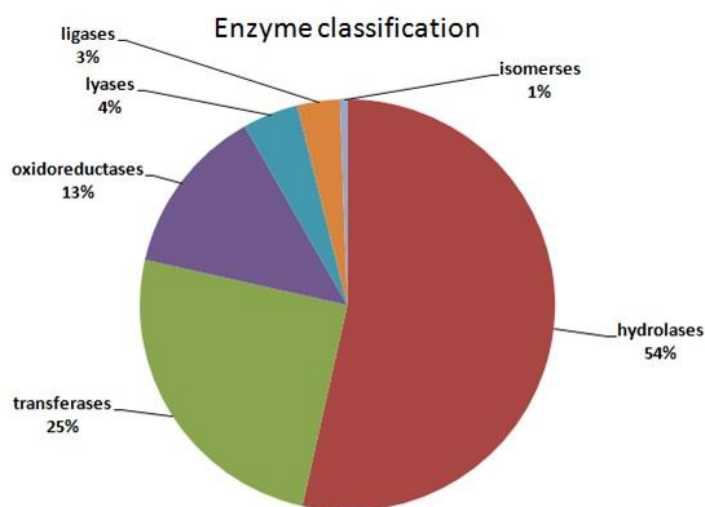


Fig. 8 Protein symmetry based classification of ACE proteins in PDB database

The classification based on protein symmetry has shown the higher in number of asymmetric (782), cyclic (534), dihedral (125), tetrahedral (20), helical (13) and Icosahedral (2) (Fig. 9).

Crystal structure of human GPX & in complex with GXpep-1 was selected for further studies based on the classifications – oxidoreductae /oxidoreductae inhibitor in *homo sapiens* of enterobacteria; expression systems is *Escherichia coli*; mutation(s) type of total 8 and PDB ID 5AMB. Structure is solved by method X-ray diffraction of resolution 1.1 Å, R-value free is 0.184 and R-value work is 0.163 (Fig. 10).

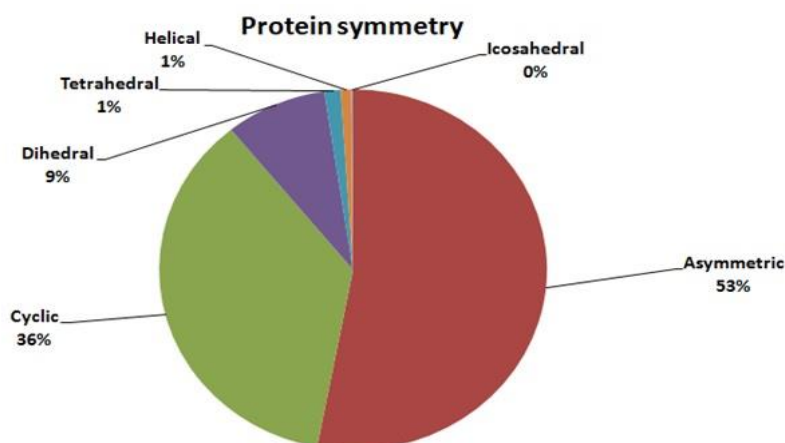


Fig. 9 The enzymatic based classification of ACE protein has shown the hydrolases (54%) is higher in this category

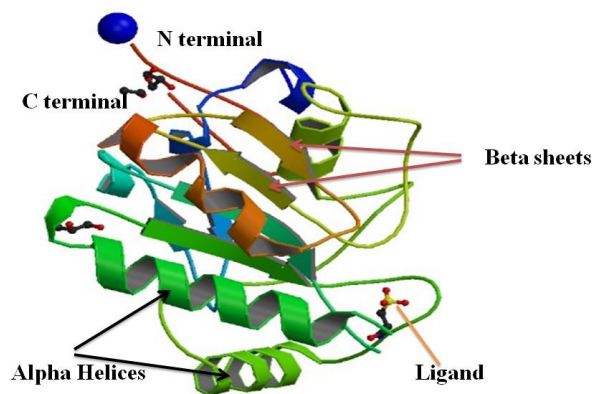


Fig. 10 3D structure of selected structure of PDB ID-5AMB

Structure of GPX4 protein

The phospholipid hydroperoxide glutathione peroxidase (GPX4) is mainly present in lipid membrane which catalyses the reaction or reduction of lipid hydroperoxides [68]. Recently, the GPX4 was investigated as a target molecule that induces iron- dependent cell death selectively in cancer cell that express mutant Ras protein. The GPX4 inhibitors are used as the potential inhibitor for the targeting novel anti-cancer drugs. To generate GPX4 inhibitors, we examined the use of peptides as an alternative to small molecules. The virtual screening of peptide libraries against T7 phages, result suggest that there is one peptide which binds to nearly 73 catalytic sites and two peptides that bind to another site of the GPX4 protein.

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