

"In silico screening of bioactive compounds derived from *Allium Sativum* Against Hypertension"

Akshada A. Koparde ^{1*}, Shreyas R. Mahadik ²

^{1*}Akshada A. Koparde Associate Professor, Department of Pharmaceutical Chemistry, Krishna Institute of Pharmacy, Krishna Vishwa Vidyapeeth (Deemed to be University), Karad, Maharashtra, India 415539

²Shreyas Mahadik, Research Student, Department of Pharmaceutical Chemistry, Krishna Institute of Pharmacy, Krishna Vishwa Vidyapeeth (Deemed to be University), Karad, Maharashtra, India 415539

*Corresponding author: Dr. Akshada A. Koparde

*Department of Pharmaceutical Chemistry, Krishna Institute of Pharmacy, Krishna Vishwa Vidyapeeth (Deemed to be University), Karad, Maharashtra, India 415439

Email: akshadkakade@gmail.com

Abstract

Hypertension is an issue of global public health that affects over 1.28 billion adults worldwide, with reports of 220 million in India alone, as reported by the World Health Organization (World Health Organization, 2021). It is a primary player in the development of cardiovascular diseases, stroke, and kidney failure. *Allium sativum* (garlic) is a commonly used medicinal plant that for years has been known for its blood pressure-lowering and heart-protective actions. This research utilized an in-silico method to analyse the possible antihypertensive effects of bioactive compounds extracted from *Allium sativum*, such as allicin, apigenin, ascorbic acid, caffeic acid, rutin, quercetin, and oleanolic acid. The phytoconstituents' 3D structures were obtained from the PubChem database. Relevant to the disease, target proteins interfacing with hypertension were found using the Therapeutic Target Database, and two pertinent receptors were chosen: angiotensin-converting enzyme (PDB ID: 1XOZ) and neprilysin (PDB ID: 6G3Q).

Molecular docking analysis was conducted with the aid of the software MolSoft ICM, employing a blind docking method for binding affinity estimation. For receptor 1XOZ, apigenin had the highest binding score of all three competitors at -26.01 kcal/mol, followed by caffeic acid and quercetin at -24.81 and -19.22 kcal/mol, respectively. For receptor 6G3Q, rutin had the highest binding affinity at -17.28 kcal/mol, followed by apigenin and caffeic acid at -16.72 and -14.96 kcal/mol, respectively. Considering the data about *Allium sativum* phytoconstituents, it seems that observable in silico interactions primarily derive from the presence of apigenin and caffeic acid. This study reinforces the notion that compounds from garlic are useful in managing hypertension and underscores the need for additional studies in vitro and in vivo.

Keywords *Allium sativum*; Hypertension; Angiotensin-converting enzyme (1XOZ); Neprilysin (6G3Q); MolSoft ICM; Quercetin.

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Introduction

Hypertension which we also refer to as high blood pressure is a very common chronic issue which affects around 1.28 billion people worldwide. It is a factor in the development of cardiovascular disease, stroke and renal problems [1]. In India we see a large-scale issue with over 220 million people affected which in turn puts forth the need for better and more accessible treatment options [2].

Like all medications, Conventional antihypertensive drugs are effective but do have some shortcomings such as side effects, making them unsuitable for some individuals. This has created a shift in attention towards other types of therapies, especially those coming from natural sources. A well-known culinary herb, *Allium sativum* (garlic), has applications in medicine too, notably for its ability to reduce blood pressure. Clinical studies have confirmed that adding garlic to one's diet can reduce systolic and diastolic blood pressure significantly, nearly as much as standard medications [3]. Garlic is known to have antihypertensive effects which are mainly due to its high content of organosulfur

*Author for Correspondence: akshadkakade@gmail.com

compounds which include allicin and S-allyl-L-cysteine. These compounds present themselves in the form of vasodilators, antioxidants, and anti-inflammatories which in turn improve vascular health [4].

In the field of computational biology, we have seen great progress which has in turn enabled the use of in silico methods like molecular docking to predict the interaction between bioactive compounds and target proteins which play a role in disease processes. This gives us a tool to screen out potential therapeutic agents before they go on to experimental validation [5].

With the aim of laying groundwork for subsequent in vitro and in vivo studies, we screened key phytoconstituents from *Allium sativum*, which includes allicin, apigenin, ascorbic acid, caffeic acid, rutin, quercetin, and oleanolic acid, for their binding affinity against the two hypertension related targets, ACE and neprilysin, using molecular docking techniques. The goal was to pinpoint constituents with significant binding affinities that could operate as possible antihypertensive candidates.

Sr. No.	Plant part	Medicinal use	Reference
1.	Bulb	Antihypertensive, Antioxidant, Antimicrobial, Cardioprotective	[6]
2.	Flower	Stimulant, anticancer, treatment for spleen enlargement, reduces VLDL & LDL cholesterol, COVID-19	[7]
3.	Leaf	Antioxidant, immunomodulatory, anti-diabetic, anti-inflammatory, antimicrobial	[8]
4.	Root	Antifungal, antiparasitic	[9]
5.	Shoot	Antioxidant, antimicrobial	[10]

Material and Methods

1. Selection of Plant and Phytoconstituents

For the purpose of this study, *Allium sativum* (popularly known as garlic) was chosen because of its well-known therapeutic value in managing heart diseases and high blood pressure [11]. It is a part of the traditional medicine due to its age-old usage, and it is known to have bioactive compounds responsible for its antihypertensive, antioxidant, and cardioprotective activities [12].

Seven significant phytoconstituents were picked for molecular docking studies which include: Allicin,

Apigenin, Ascorbic acid, Caffeic acid, Rutin, Quercetin, and Oleanolic acid [13].

The selection was based on the presumed therapeutic possibilities these compounds held along with their noted presence in garlic, especially the bulb section [14]. The therapeutic components have known biological activities like inflammation and oxidation inhibition, as well as dilation of blood vessels which can help manage blood pressure [15].

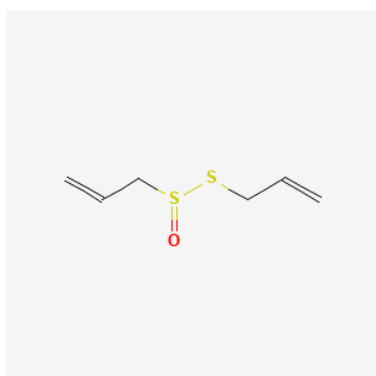


Figure 1: - Allicin

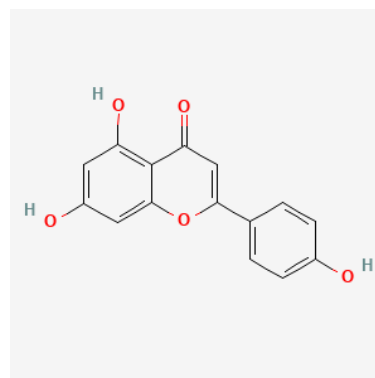


Figure 2: - Apigenin

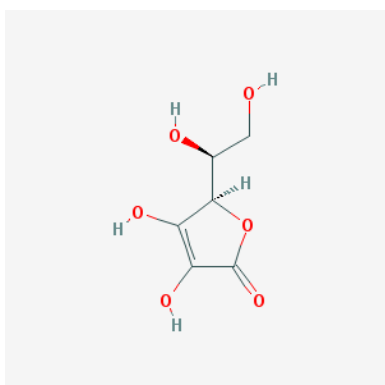


Figure 3: - Ascorbic Acid

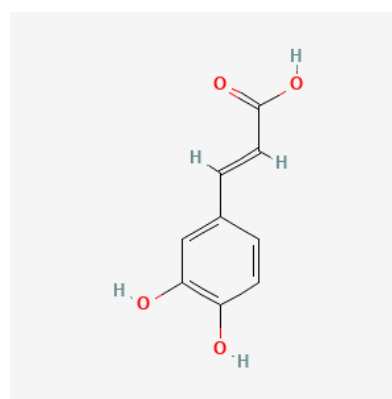


Figure 4: - Caffeic Acid

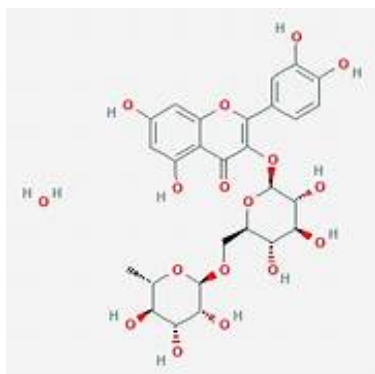


Figure 5: - Rutin

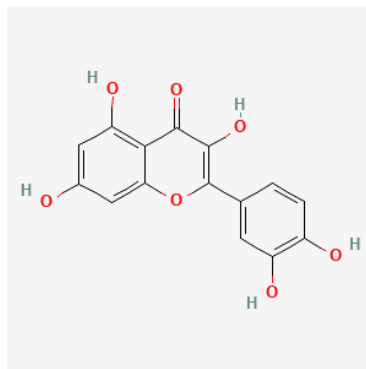


Figure 6: - Quercetin

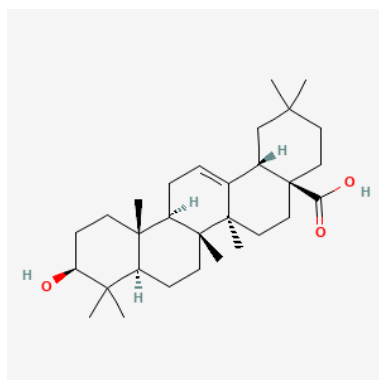


Figure 7: - Oleanolic Acid

2. Retrieval of Ligand Structures

Chemical structures of the chosen phytoconstituents: allicin, apigenin, ascorbic acid, caffeic acid, rutin, quercetin, oleanolic acid, were retrieved from the chemical information repository known as the PubChem database. It is a freely accessible and trusted source of chemical information [16].

Molecular editing tools were employed to change the structures' format from .SDF to .pdb, which is compatible with the MolSoft docking software [17]. To enhance the interaction with the target proteins, the ligand molecules were energy minimized with their 3D geometry optimized prior to docking and interacting with the target proteins to meet the docking requirements [18].

3. Selection of Target Proteins

To identify protein targets relevant to hypertension, we utilized the Therapeutic Target Database (TTD) [19]. The two protein targets chosen were 1XOZ and 6G3Q due to their relevance to hypertension. These proteins are part of pathways that contribute to the regulation of blood pressure [20].

The 3D crystal structures of the proteins in question were obtained from the Protein Data Bank (PDB) in .pdb format [21]. We then used MolSoft software to prepare these files for docking which included a step of removing water molecules, adding hydrogen atoms, and also protein structure optimization all of which we did to make sure for accurate ligand binding during the docking process [22].

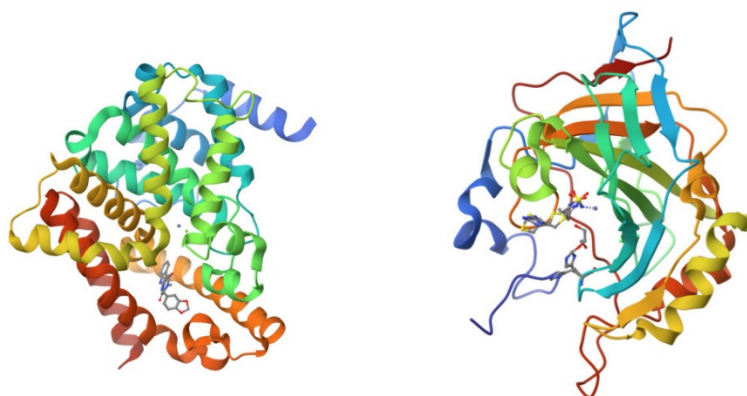


Figure 8: - 1XOZ

4. Docking Procedure

For our molecular docking studies, we used the software MolSoft ICM-Pro [23]. Both the prepared ligands, which consisted of the phytoconstituents of Allium sativum, as well as the target proteins (PDB IDs 1XOZ and 6G3Q) were input to the software [24]. In order to map possible binding sites, a blind docking approach was used to scan the entirety of the protein surface [25]. During docking,

Figure 9: - 6G3Q

phytoconstituents were free to move, while the protein remained static. No other modifications to the default settings were made, except those specified in the text. To assess the binding affinities of the various phytoconstituents with the target receptors, the docking scores were analysed as binding affinity metrics [26].

Result & discussion

1. Ramchandran plot

A. 1XOZ

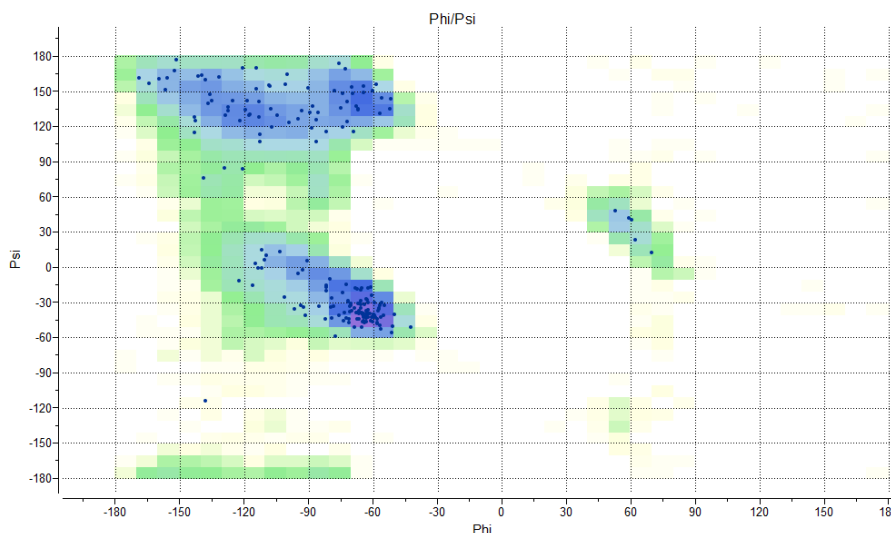


Figure 10: - Ramachandran Plot of the Angiotensin-Converting Enzyme (1XOZ) in Complex with Apigenin

1XOZ had been assessed through use of a Ramachandran plot which was generated in MolSoft. In that plot the large part of the amino acid residues were in the most favoured areas, which correspond to very stable conformations such as beta sheets and right handed alpha helices. Also, some of the residues fell into the also allowed regions that while not as preferred still include flexible or less common conformations. Only a

few residues were seen in the disallowed regions which is an indication of a very well refined and structurally stable protein which is also suited for docking analysis. This study reports that we have confirmed the receptor structure's validity and that the results of the docking we did are reliable for the evaluation of the binding interactions of Allium sativum phytoconstituents with the hypertension related target.

Colour Region	Description	Residual Quality	Typical Residue Percentage	Structural Implication
Green	Most favoured	Excellent, stable backbone	>90%	Properly folded, reliable protein
Yellow/Yellowish	Additionally allowed	Acceptable with some strain	5 - 10 %	Flexible regions, loops or turns
Blue/Outliers	Disallowed or outliers	Unfavorable or strained	<2%	Possible errors or special; review

B. 6G3Q

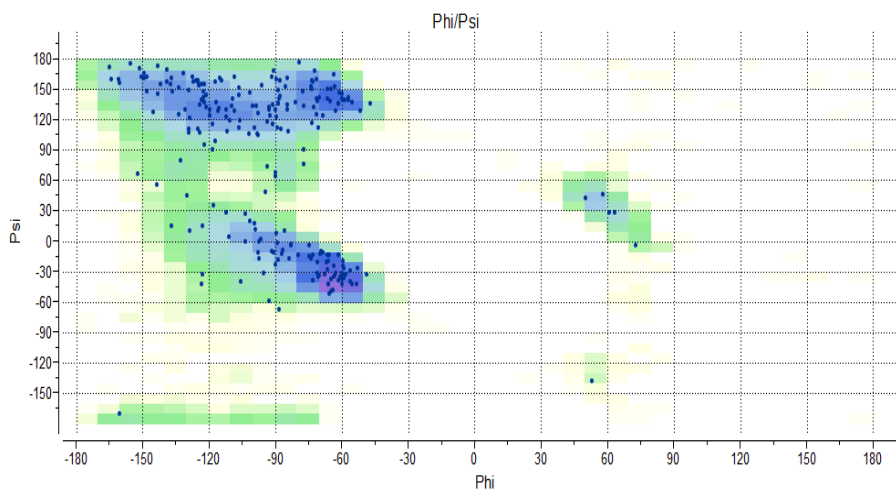


Figure 11: - Ramachandran Plot of Nephilysin (6G3Q) in Complex with Apigenin

The Ramachandran plot from the protein structure analysis shows that most of the amino acid residues lie within the highly favoured regions, mostly involving stable secondary structures like right-handed α -helices and β -sheets. The presence of these regions indicates the dense accumulation of residues in favourable energetic conformations, which suggests a well-folded and structural stability of the protein. A lesser portion of residues are discovered in the additionally allowed regions which usually identify energetic loop regions of

greater flexibility or less common backbone conformations that are still permissible. Disallowed regions are populated by only a minimal number of residues suggesting some rare or strained conformations which may be due to specific amino acids like glycine or proline, or possibly some modelling artifacts. In general, the residue distribution in this plot supports the claim that the model of the protein is accurate and that it can be utilized for docking studies on molecular structures reliably.

Colour Region	Description	Residual Quality	Typical Residue Percentage	Structural Implication
Green	Most favoured region	Stable secondary structure	>90%	Well folded polypeptides and trustable proteins
Yellow/Yellowish	Additionally allowed	Flexible loops or turns	5-10%	Flexible regions or turns
Blue/Outliers	Disallowed/outliers	Possible errors or flexible residues	<2%	Possible special cases or errors; pending review

1. Visualization of Molecular Docking

A. 1XOZ

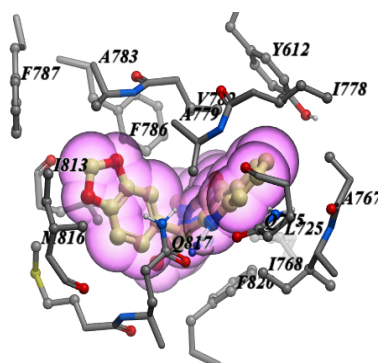


Figure 12: - Molecular Docking Visualization of Apigenin within the Active Site of Angiotensin-Converting Enzyme (PDB ID: 1XOZ)

The given docking image shows the interaction of a phytoconstituent with human angiotensin converting enzyme (ACE) which is also known as the 1XOZ receptor. The ligand which is to include compounds like quercetin or apigenin is presented as it binds into the receptors active site. Also of note are key amino acid residues which play a role in the interaction including hydrophobic and aromatic residues along with polar ones. The ligand is very well fit in the binding pocket as

seen in the pink molecular surface which in turn reports a very stable and strong binding affinity. Also, these interactions may play a role in the inhibition of the enzymatic activity of ACE which in turn reduces angiotensin II production and thus we see to it that we have antihypertensive effects. This also brings to the fore the fact that the phytoconstituent in question has great potential as a natural ACE inhibitor in the issue of high blood pressure.

B. 6G3Q

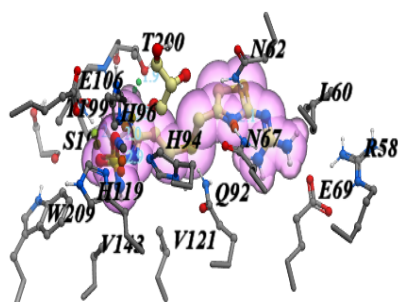


Figure 13: - Molecular Docking Visualization of Apigenin within the Active Site of Neprilysin (PDB ID: 6G3Q)

Providing a picture of what we see is a phytoconstituent's interaction with the 6G3Q receptor which is a part of the natriuretic peptide receptor pathway that includes blood pressure regulation. The ligand which is to which the like of Allium sativum's active components like rutin or oleanolic acid affixes itself in a very defined binding pocket within the receptor. It is surrounded by key residues which include histidine's, polar and charged residues. These residues

enhance ligand bonding through hydrogen bonding, hydrophobic interactions, and π - π stacking. The pink molecular surface highlights the extent and location of interaction. Strong and specific interaction like these indicate that the ligand is capable of modulating receptor activity which aids in either vasodilation or natriuresis, thus reinforcing its proposed action in antihypertensive treatment.

2. Binding energy

Sr. No.	Phytoconstituent	1XOZ	6G3Q
1.	Allicin	-15.75	-6.242
2.	Apigenin	-26.01	-16.72
3.	Ascorbic acid	-14.08	-2.026
4.	Caffeic acid	-24.81	-14.96
5.	Rutin	-7.25	-17.28
6.	Quercetin	-19.22	-13.54
7.	Oleanolic acid	-0.613	-11.92

From the medicinal plant Allium sativum (garlic), we use its

phytochemicals to create a ligand-based model of pharmacophores. The structures of allicin, apigenin, ascorbic acid, caffeic acid, rutin, quercetin, and oleanolic

acid were retrieved from PubChem and prepared for docking. The ligands were also selected with respect to the docking sites. Target proteins related to hypertension were obtained from the Protein Data Bank (PDB) with the PDB IDs: 1OXZ and 6G3Q. These proteins are known to have some roles in the development of hypertension.

The chosen compounds have showed as having remarkable binding energies with Apigenin and Caffeic acid demonstrating the best interaction profiles against both receptor targets. Apigenin showed the greatest binding with 1OXZ (−26.01 kcal/mol) and 6G3Q (−16.72 kcal/mol) suggesting high potential for antihypertensive activity. *Allium sativum* has been known as a medicinal herb of great importance for many years, and was used in the treatment of hypertension, cardiovascular diseases, and inflammation. Its use in modern medicine is justified by the bioactive constituents of the plant, which might be potential antihypertensives. Garlic is also a natural medicine as it has antioxidant, lipid lowering, and vasodilatory properties.

Conclusion: -

This study looked into the antihypertensive activity effects of *Allium sativum* by performing molecular docking of its key phytoconstituents—allicin, apigenin, ascorbic acid, caffeic acid, rutin, quercetin, oleanolic acid—with the receptors, 1OXZ and 6G3Q which are of hypertension's interest. The respective ligands were constructed based on the information retrieved from PubChem and the docking was performed in MolSoft using a blind docking technique. Out of the tested compounds, the highest binding affinity of apigenin was with 1OXZ, while 6G3Q was best docked with caffeic acid, apigenin's counterpart. These results indicated that both proteins were strongly interacted with.

Other reports show that quercetin and oleanolic acid also did well which in turn supports the use of *Allium sativum* in treatment of hypertension as per tradition. We put forth that its phytochemicals may be that which will inform the development of future antihypertensive drugs. At the same time, it is important to note that we still need more research in vitro and in vivo to prove out the therapeutic value and safety of these compounds.

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