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Integrated in Silico Docking and ADMET Investigation of Quercetin Targeting Angiotensin-Converting Enzyme

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Abstract:
Hypertension is a major cardiovascular disorder mainly regulated by the Renin–Angiotensin–Aldosterone System. Angiotensin-Converting Enzyme converts angiotensin I into angiotensin II, which increases blood pressure. Captopril is a commonly used ACE inhibitor, but its long-term use may cause side effects. Therefore, natural phytoconstituents such as Quercetin are being studied as safer alternatives.
The present study aimed to evaluate the ACE inhibitory activity of quercetin using molecular docking and compare it with captopril. Docking studies were performed using PyRx and interaction analysis was carried out using Discovery Studio Visualizer. Results showed that quercetin exhibited good binding affinity with ACE and formed stable hydrogen bond interactions with active site amino acid residues, similar to captopril.
The study suggests that quercetin may act as a potential natural ACE inhibitor and could be useful in the management of hypertension. Further in vitro and in vivo studies are required to confirm its therapeutic efficacy and safety.
The docking analysis demonstrated that quercetin exhibited significant binding affinity toward the active site of ACE, showing stable interactions with important catalytic amino acid residues comparable to those of captopril. Quercetin formed multiple hydrogen bonds and hydrophobic interactions within the ACE active pocket, suggesting strong inhibitory potential. The obtained docking score indicated favorable ligand–receptor interaction and supported the possibility of quercetin acting as a natural ACE inhibitor. Comparative analysis revealed that quercetin may possess promising antihypertensive activity with fewer side effects due to its natural origin and antioxidant properties.

Keywords: Molecular docking, Hypertension, Angiotensin Converting Enzyme, ACE inhibitor, Captopril, Quercetin, PyRx, Auto dock Vina, Phytoconstituents, Drug Discovery.

1. Introduction

Hypertension is a major cardiovascular disorder regulated by the Renin–Angiotensin–Aldosterone System (RAAS). The Angiotensin-Converting Enzyme (ACE) plays a key role by converting angiotensin I into angiotensin II, a potent vasoconstrictor that increases blood pressure. Therefore, inhibition of ACE is an important therapeutic strategy in the management of hypertension.
Conventional ACE inhibitors such as Captopril and Enalapril effectively reduce blood pressure by blocking ACE activity. However, these drugs are associated with adverse effects like dry cough and angioedema, which limits their long-term use.
The standard ACE inhibitor drug commonly used is Captopril. Recent research has also focused on natural phytoconstituents such as Quercetin because of their antioxidant and antihypertensive activities.

Angiotensin I → Angiotensin II

Among ACE inhibitors, Captopril was the first orally active ACE inhibitor introduced for the treatment of hypertension and cardiovascular diseases. Captopril reduces blood pressure by inhibiting ACE activity, thereby decreasing the formation of angiotensin II and reducing aldosterone secretion. This results in vasodilation, decreased sodium and water retention, and reduced cardiac workload. It is widely used in hypertension, congestive heart failure, diabetic nephropathy, and myocardial infarction management. However, long-term use of captopril may produce adverse effects such as dry cough, taste disturbances, skin rashes, hypotension, and renal impairment.

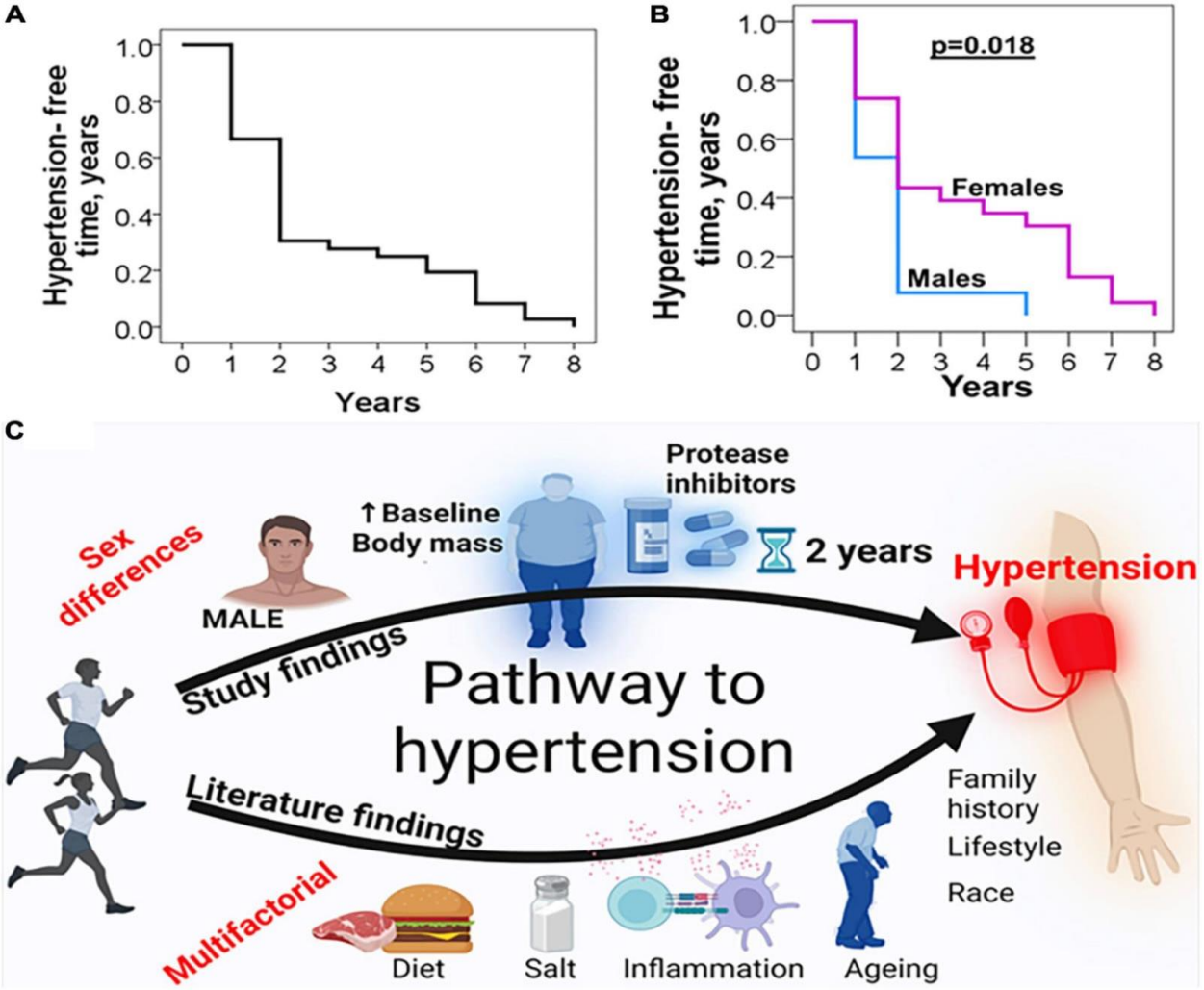
❖ **Blood Pressure Regulation and RAAS System:**

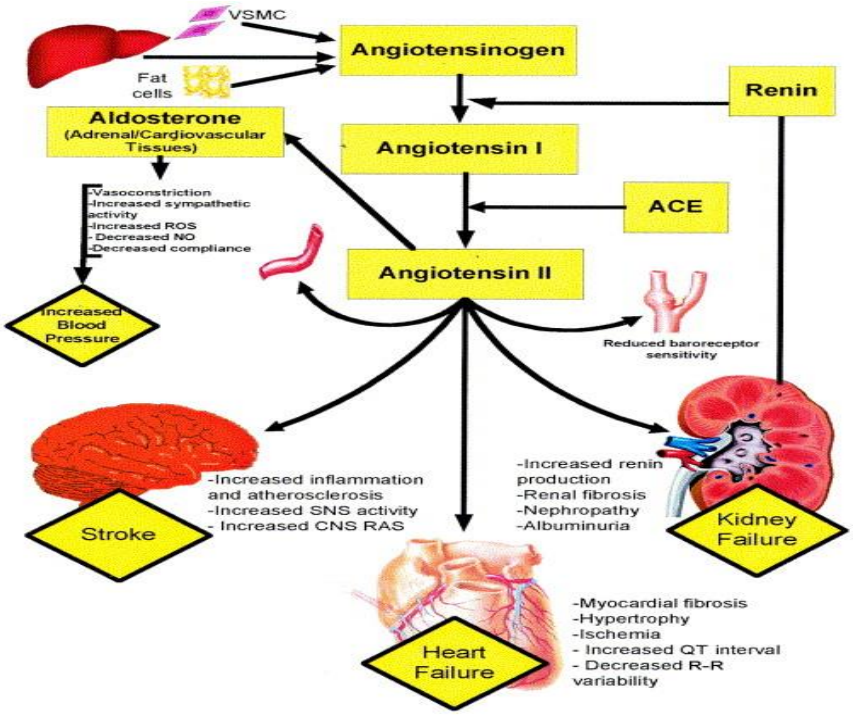
- **What is Blood Pressure?**

Blood pressure is the force exerted by circulating blood on the walls of arteries.

- **Normal blood pressure**:
  - Systolic: 120 mmHg
  - Diastolic: 80 mmHg

When blood pressure increases continuously, it causes hypertension. Hypertension is one of the major risk factors for cardiovascular diseases, stroke, kidney failure, and heart failure[1]





❖ **Pathophysiology of Hypertension**

The pathophysiology of hypertension mainly involves increased peripheral vascular resistance and abnormal regulation of blood pressure by neural, renal, hormonal, and vascular mechanisms.

1. Increased Peripheral Resistance

Narrowing or constriction of blood vessels increases resistance to blood flow, leading to elevated arterial pressure.

2. Overactivation of the Renin–Angiotensin–Aldosterone System (RAAS)

The kidneys release renin when blood flow decreases. Renin converts angiotensinogen into angiotensin I, which is further converted into angiotensin II by Angiotensin-Converting Enzyme (ACE).

Angiotensinogen —Renin→ Angiotensin I —ACE→ Angiotensin II

Angiotensin II is a potent vasoconstrictor that:

- Constricts blood vessels
- Increases blood pressure
- Stimulates aldosterone secretion
- Promotes sodium and water retention

This results in increased blood volume and sustained hypertension.

3. Sympathetic Nervous System Activation

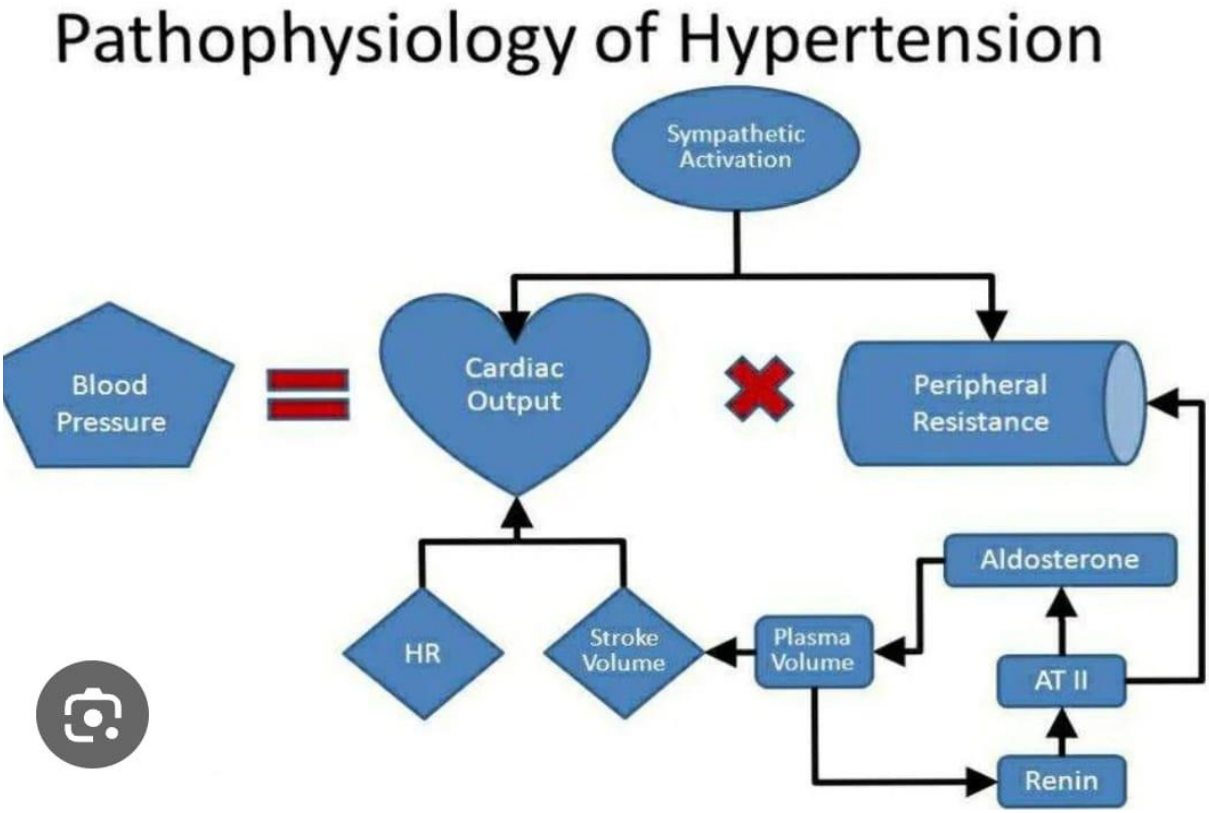
Excess sympathetic stimulation increases heart rate and vasoconstriction, causing elevated cardiac output and blood pressure.

4. Endothelial Dysfunction

Reduced production of nitric oxide and increased oxidative stress impair blood vessel relaxation, contributing to hypertension.

5. Sodium and Water Retention

Excess retention of sodium and water by the kidneys increases blood volume and cardiac workload [2].



❖ **Mechanism of ACE Inhibitors**

Captopril and other ACE inhibitors act by inhibiting the Angiotensin-Converting Enzyme (ACE), an important enzyme in the Renin–Angiotensin–Aldosterone System (RAAS), which regulates blood pressure and fluid balance.

▪ ***Stepwise Mechanism of Action***

1. Release of Renin

When blood pressure decreases, the kidneys release renin.

2. Formation of Angiotensin I

Renin converts angiotensinogen into angiotensin I.

Angiotensinogen —(Renin)→ Angiotensin I

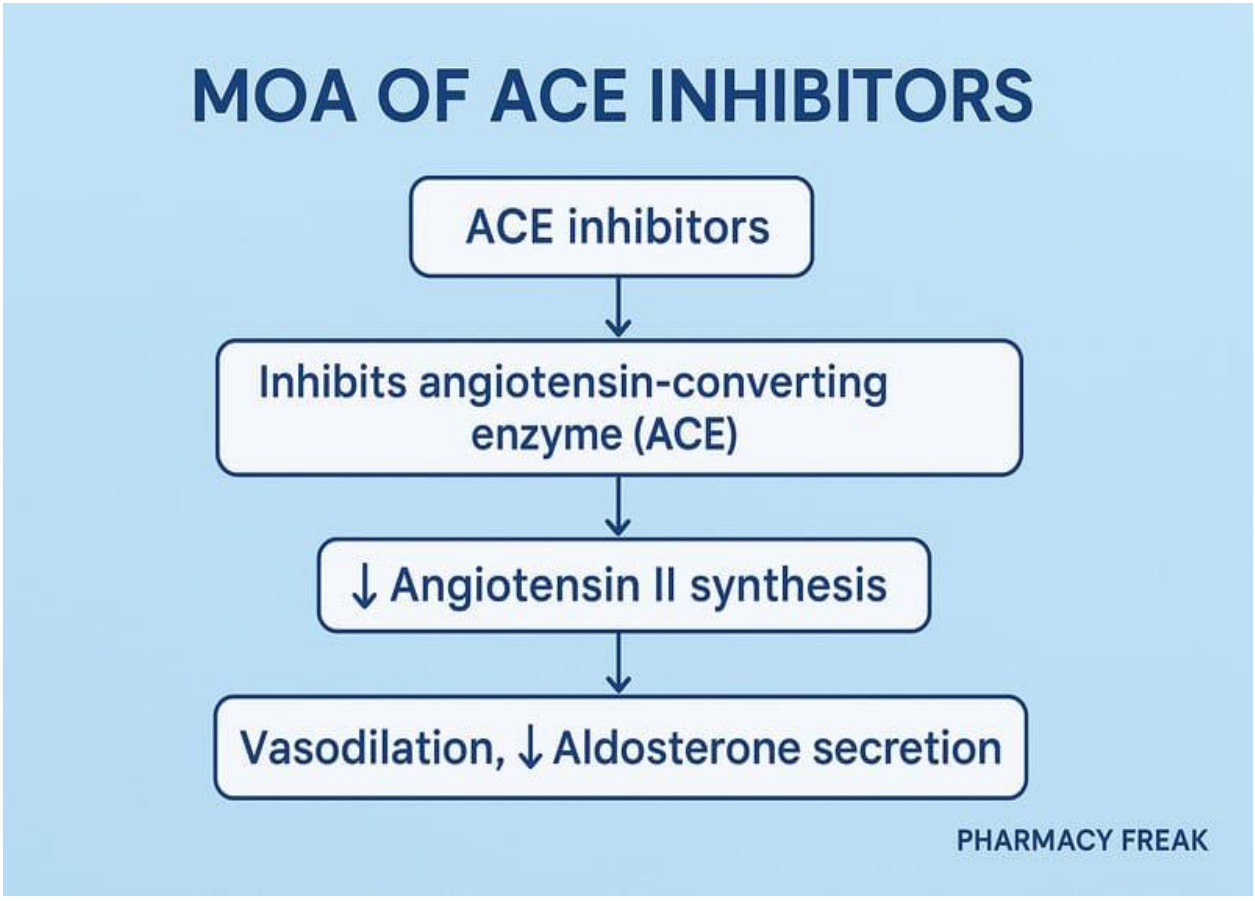
3. Conversion of Angiotensin I into Angiotensin II

Normally, ACE converts angiotensin I into angiotensin II.

Angiotensin I —(ACE)→ Angiotensin II

Angiotensin II:

- Causes vasoconstriction
- Increases aldosterone secretion
- Promotes sodium and water retention
- Raises blood pressure[3]



❖ **Molecular Docking:**

Molecular docking is a computer-aided drug design technique used to predict how a ligand (drug or phytoconstituent) binds with a target protein or receptor. It helps in identifying the binding affinity, interaction energy, and orientation of molecules at the active site of a protein. Molecular docking is widely used in pharmaceutical research to discover new drugs and phytochemicals for diseases such as hypertension, diabetes, cancer, and infections[4].

- **Principle of Molecular Docking**

The docking process involves:

1.Selection of target protein

Example: Angiotensin Converting Enzyme (ACE) in hypertension.

2.Preparation of ligand

Example: Quercetin or Captopril.

3.Binding interaction analysis

The software predicts hydrogen bonds, hydrophobic interactions, and binding energy.

4.Scoring function

Lower binding energy indicates stronger interaction and better stability of ligand–protein complex[4].

- **ACE and Hypertension**

Blood pressure increases mainly because of activation of the Renin-Angiotensin-Aldosterone System (RAAS).

▪ ***Pathway of Blood Pressure Increase***

Low blood flow to kidney
↓
Renin release
↓
Angiotensinogen → Angiotensin I

↓ (ACE enzyme)
Angiotensin II formation
↓
Vasoconstriction + Aldosterone release
↓
Sodium & water retention
↓
Increased Blood Pressure

ACE converts Angiotensin I into Angiotensin II, a potent vasoconstrictor that increases blood pressure. ACE inhibitors block this conversion and reduce hypertension[5].
Inline formula for ACE inhibition mechanism:

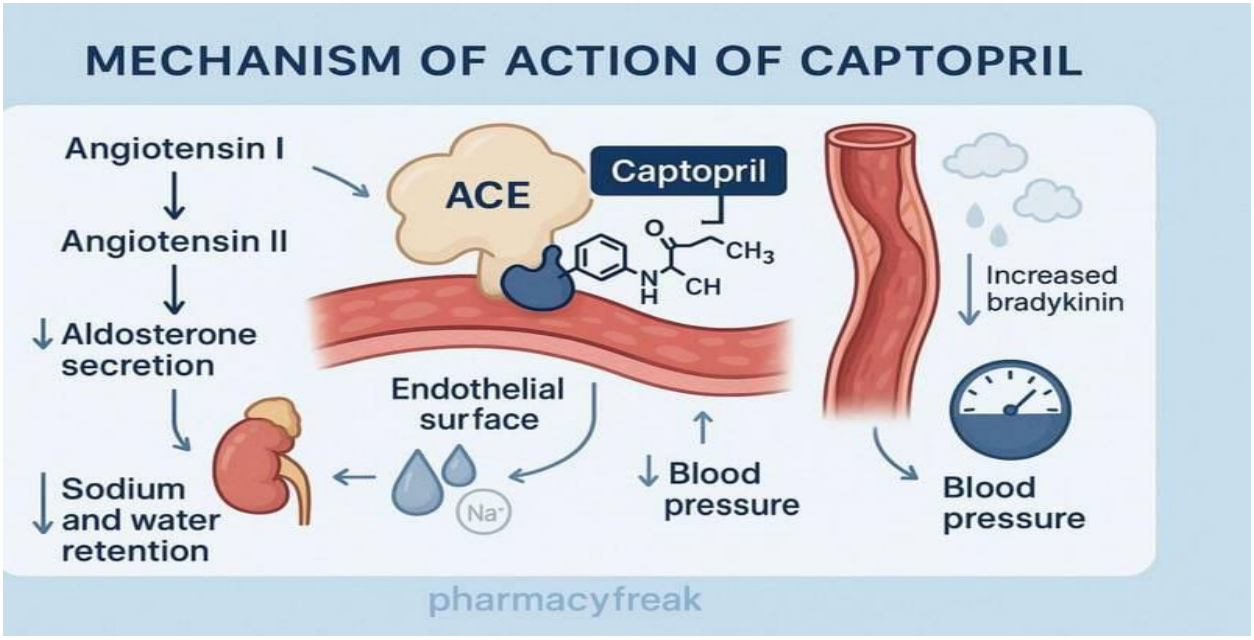
$$\text{Angiotensin I} \xrightarrow{\text{ACE}} \text{Angiotensin II}$$

- ***What is Captopril?***

Captopril is a synthetic ACE inhibitor used for treatment of hypertension, heart failure, and kidney disorders.

- ***Mechanism of Captopril***

Inhibits ACE enzyme competitively.
↓
Reduces formation of Angiotensin II.
↓
Causes vasodilation
↓
Decreases aldosterone secretion.
↓
Lowers sodium and water retention.
↓
Finally decreases blood pressure[5]



❖ **Why Quercetin is Preferred as a Phytoconstituent Over Captopril in Molecular Docking**

Quercetin is a naturally occurring flavonoid found in onions, apples, berries, tea, and many medicinal plants.

- **Reasons for Preference of Quercetin**

1. Natural Phytoconstituent

Quercetin is plant-derived and considered safer with lower toxicity compared to synthetic drugs. It is widely studied for cardiovascular protection.

2. Strong Antioxidant Activity

Quercetin scavenges free radicals and reduces oxidative stress, which contributes to hypertension and cardiovascular damage.

3. Anti-Inflammatory Effect

It inhibits inflammatory mediators and protects blood vessels.

4. ACE Inhibitory Potential

Docking studies show that quercetin can bind effectively to ACE active sites through hydrogen bonding and hydrophobic interactions.

5. Multi-Target Action

Unlike captopril which mainly inhibits ACE, quercetin shows:

- antioxidant activity
- vasodilatory action
- anti-inflammatory effects
- endothelial protection

6. Reduced Side Effects

Captopril may produce:

- dry cough
- hyperkalemia
- angioedema
- taste disturbances

Quercetin generally has fewer adverse effects in experimental studies[5,6]

❖ **Comparison Between Quercetin And Captopril:**

Feature	**Quercetin**	**Captopril**
Source	Natural phytoconstituents	Synthetic drug
Chemical Class	Flavonoid	ACE inhibitor
Main Action	Antioxidant+ACE inhibition	ACE inhibition
Mechanism	Multi target cardiovascular protection	Competitive ACE inhibition
Side Effects	Comparatively less	Cough, Hyperkalemia
Additional benefits	Anti inflammatory, Antioxidant	Mainly antihypertensive
Use in Docking	Novel phytotherapeutic Candidate	Standard Referance Drug
Binding To ACE	Strong Hydrogen bonding	Standard ACE binding

2. Aims And Objectives

❖ **Aims:**

To perform molecular docking studies of the phytoconstituent Quercetin with the Angiotensin Converting Enzyme (ACE) and compare its binding affinity, interaction pattern, and antihypertensive potential with the standard ACE inhibitor Captopril for the management of hypertension.ACE plays an important role in the Renin-Angiotensin-Aldosterone System (RAAS) by converting Angiotensin I into Angiotensin II, which increases blood pressure through vasoconstriction and aldosterone release. Therefore, inhibition of ACE is an important therapeutic target in hypertension management[7]

Quercetin, a naturally occurring flavonoid, possesses antioxidant, anti-inflammatory, and cardiovascular protective activities, making it a potential alternative phytoconstituent for antihypertensive therapy. Molecular docking helps predict ligand-protein interactions and binding stability between quercetin and ACE enzyme.

❖ **Objectives:**

1. To study the pathophysiology of hypertension

- To understand the role of the Renin-Angiotensin-Aldosterone System (RAAS) in increasing blood pressure.
- To study the conversion of Angiotensin I into Angiotensin II by ACE enzyme.
- To evaluate how vasoconstriction and aldosterone release contribute to hypertension[7,8]

2. To perform molecular docking studies of Quercetin with ACE enzyme

- To analyze ligand–protein interaction between quercetin and ACE.
- To identify hydrogen bonding and binding interactions at the active site of ACE.
- To determine docking score and binding affinity of quercetin[9,10]

3. To compare Quercetin with standard drug Captopril

- To compare docking energy values of quercetin and captopril.
- To evaluate the similarity of binding interactions with ACE enzyme.
- To assess whether quercetin can act as a potential ACE inhibitory compound[11,12]

4. To evaluate antihypertensive potential of Quercetin

- To investigate ACE inhibitory activity of quercetin.

- To study the role of quercetin in lowering blood pressure[13,14].

5. To identify natural phytoconstituents as safer alternatives

- To evaluate the therapeutic advantages of plant-derived compounds over synthetic drugs.
- To compare adverse effects of quercetin and captopril.
- To explore natural compounds with lower toxicity and better safety profile[15].

6. To study ligand–protein complex stability

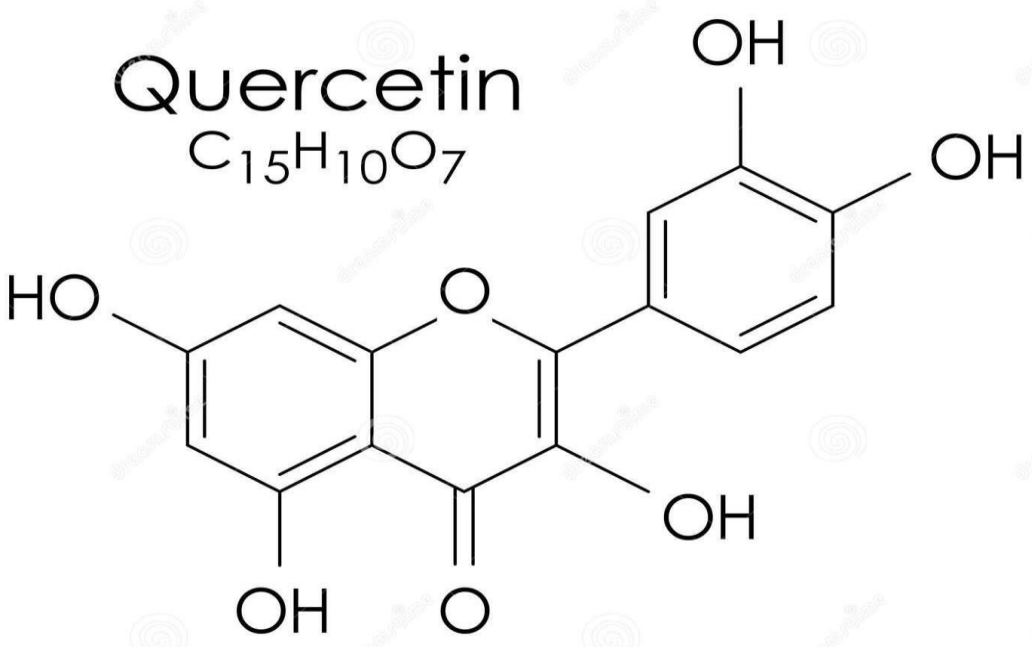
- To determine amino acid residues involved in ACE inhibition.
- To evaluate stability of quercetin-ACE complex through molecular interaction studies.
- To predict biological activity using computational methods[16]

3. LITERATURE REVIEW

1.Introduction to Quercetin:

Quercetin is a naturally occurring polyphenolic flavonoid widely present in fruits and vegetables such as apples, onions, and berries. It has gained attention due to its cardioprotective, antioxidant, anti-inflammatory, and antihypertensive properties.

Epidemiological studies suggest that higher dietary intake of quercetin is associated with a reduced risk of cardiovascular diseases, including hypertensi·[17,18]



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2.Classification of Quercetin

2.1 Chemical Classification

Quercetin is classified as:

- ✓ **Class**: Flavonoids
- ✓ **Subclass**: Flavonols
- ✓ **Type**: Polyphenolic compound

Flavonoids are a large class of plant secondary metabolites, and quercetin specifically belongs to the flavonol subclass, characterized by a hydroxyl group at position 3 of the flavonoid skeleton.

2.2 Structural Classification

Quercetin has the following structural features:

- Basic flavonoid structure: Two aromatic rings (A and B) connected by a three-carbon bridge forming a heterocyclic ring (C)
- Contains five hydroxyl (–OH) groups at positions 3, 5, 7, 3′, and 4′
- Chemical formula: $C_{15}H_{10}O_7$

These hydroxyl groups are responsible for its strong antioxidant activity and biological functions .

3.Natural Sources of Quercetin

Quercetin is widely distributed in:

- Fruits: apples, berries
- Vegetables: onions, broccoli, cabbage
- Beverages: tea, wine
- Herbs and medicinal plants

It is considered one of the most common flavonoids in the human diet.

4. Physicochemical Properties

- Color: Yellow crystalline compound
- Solubility:Soluble in alcohol and lipids Poorly soluble in water
- Stability: Sensitive to heat and light

These properties influence its bioavailability and pharmacological use .

5. Derivatives and Forms of Quercetin

Quercetin occurs in different forms:

- Aglycone form (pure quercetin)
- Glycosides (e.g., rutin, isoquercetin)
- Methylated and sulfated derivatives

Attachment of sugar molecules (glycosylation) affects its absorption and biological activity.

6. Pharmacological Importance

Quercetin exhibits multiple biological activities:

- Antioxidant,Anticancer
- Anti-inflammatory, Antiviral
- Antihypertensive (ACE inhibition-related)

These properties make it a promising candidate in drug discovery and molecular docking studies [19.1,19.2]

7. Antihypertensive Activity

Quercetin helps lower blood pressure by:

- Relaxing blood vessels
- Reducing oxidative stress [20,21]

8. Quercetin as an ACE Inhibitor

8.1 What is ACE?

ACE (Angiotensin-Converting Enzyme) increases blood pressure by producing angiotensin II.

8.2 Role of Quercetin

Quercetin acts as a natural ACE inhibitor:

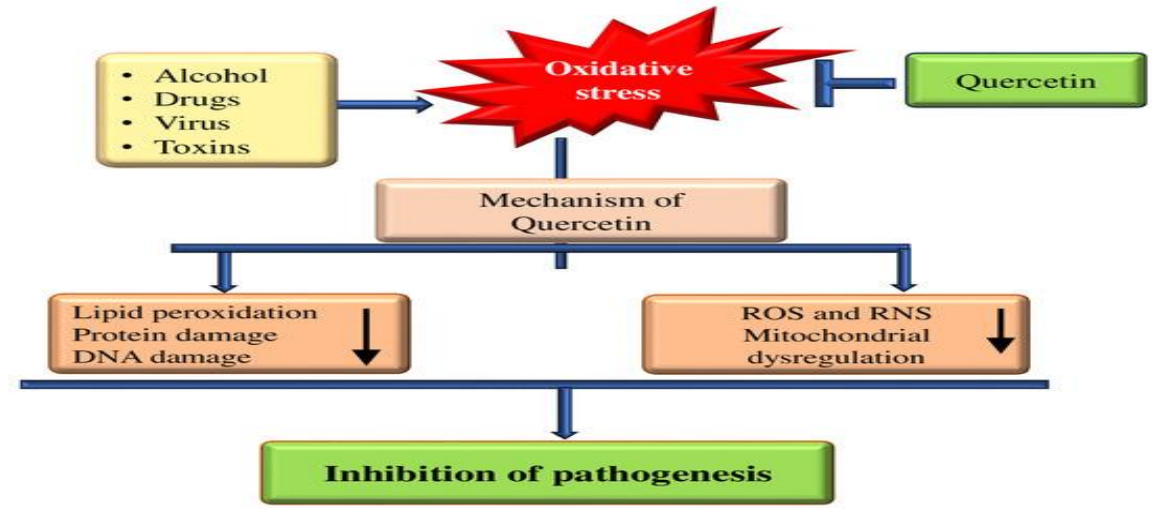
- Blocks ACE enzyme activity
- Reduces angiotensin II formation
- Causes blood vessel relaxation

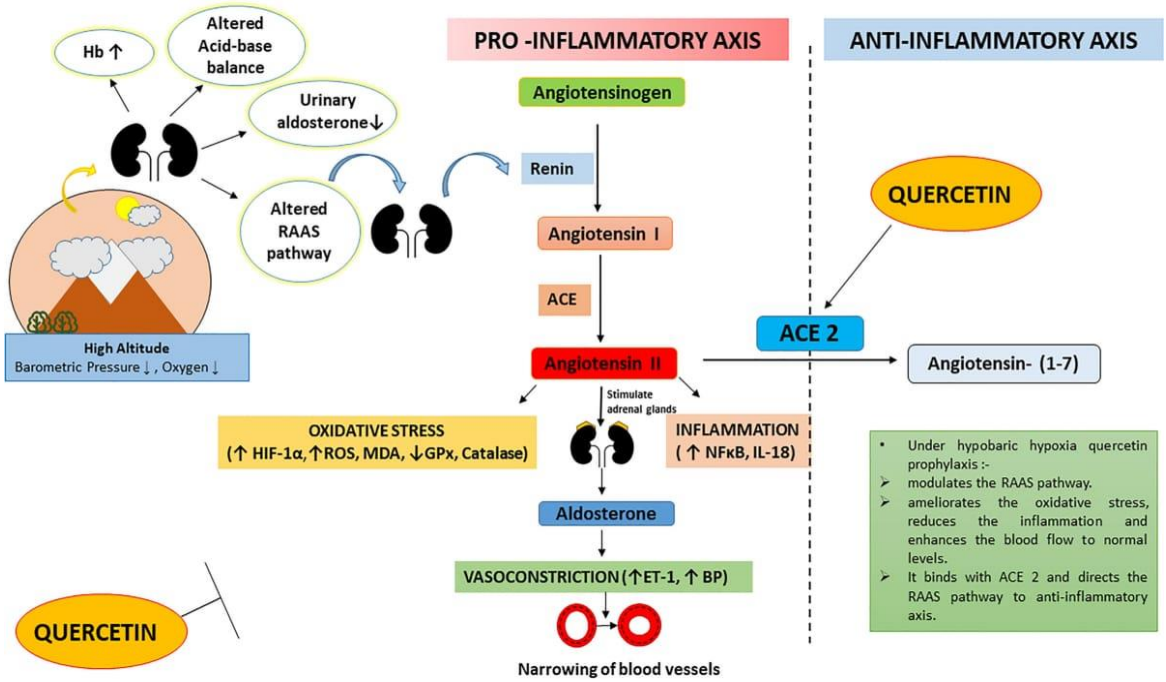
This leads to lower blood pressure[20,21]

8.3 Mechanism of Action

Quercetin works in different ways:

1. Directly inhibits ACE enzyme
2. Increases nitric oxide → causes vasodilation
3. Reduces oxidative stress
4. Improves endothelial function[20]
5.





9. Advantages of Quercetin

- ✓ Natural compound
- ✓ Fewer side effects compared to synthetic drugs
- ✓ Multiple health benefits
- ✓ Easily available in diet.[22]

10. Limitations of Quercetin

- ✓ Low bioavailability
- ✓ Poor water solubility
- ✓ Needs high dose for effect
- ✓ Limited clinical trials[23]

11. Application in Molecular Docking

Quercetin is widely used in molecular docking studies because:

1. It binds strongly to ACE enzyme
2. Shows good binding energy
3. Acts similar to drugs like captopril.[24]

4. METHODOLOGY

1.Study Design :

Molecular docking is an in silico technique used to predict the binding interaction between a ligand (Quercetin) and a target protein (ACE). It helps evaluate binding affinity and inhibitory potential.The **aim of this study** is to evaluate the binding affinity and interaction pattern of Quercetin with Angiotensin-Converting Enzyme (ACE) and compare it with standard ACE inhibitors such as Captopril.ACE is responsible for converting angiotensin I to angiotensin II, which increases blood pressure. Inhibition of ACE is a key therapeutic strategy in hypertension.

Molecular docking is a computational drug discovery technique used to predict the interaction between a ligand and a target protein. It helps determine:

- binding affinity
- binding orientation
- intermolecular interactions
- stability of ligand–protein complex

In hypertension, the Angiotensin Converting Enzyme (ACE) is an important therapeutic target because it converts Angiotensin I into Angiotensin II, which causes vasoconstriction and increases blood pressure. ACE inhibitors such as captopril block this conversion and reduce hypertension

2. Objectives:

i. To obtain ACE protein structure from Protein Data Bank (PDB).
ii. To obtain quercetin and captopril ligand structures from PubChem.
iii. To prepare protein and ligands for docking.
iv. To perform molecular docking using PyRx software.
v. To analyze ligand–protein interactions using Discovery Studio.
vi. To compare docking score and binding affinity of quercetin and captopril.

3. Software And Tools Required:

Software/Database	**Version**	**Purpose**
PyRx	Version 0.8	Molecular Docking
AutoDock Vina	Integrated in PyRx	Docking engine
Discovery Studio Visualizer	Version 2021 or 2020	Visualization of interaction
Protein Data Bank (PDB)	Online database	Protein structure download
PubChem	Online database	Ligand structure download
Open Babel	Integrated in PyRx	File Conversion
Pymol	Version 2.5	Protein Visualization
SwissADME	Web Server	ADMET Prediction
ProTox-II	Version 3.0	Toxicity Prediction
pkCSM	Web Server	Pharmacokinetics

4.Hardware Requirements:

Requirements	Specifications
Processor	Intel i3/i5 or above
RAM	Minimum 4 GB
Operating System	Window 10/11
Storage	Minimum 10 GB free space

5.Databases Used

A. Protein Data Bank (PDB)

The Protein Data Bank is used for downloading the three-dimensional crystal structure of proteins.

Website:

➢ Protein Data Bank (PDB)

Protein Selected

- ACE enzyme
- Example PDB ID: 1O86

Reason for Selection

- High resolution structure
- Proper active site
- Presence of ACE inhibitory complex

B. PubChem Database

PubChem is used for downloading ligand structures.

Website:

➢ PubChem

Ligands Used

1. Quercetin
2. Captopril

6.Methodology*:*

The methodology of molecular docking involves systematic computational procedures for studying the interaction between ligands (Quercetin and Captopril) and the target protein Angiotensin Converting Enzyme (ACE). The complete docking process includes protein preparation, ligand preparation, active site identification, docking simulation, and interaction analysis.

6.1 Selection of Target Protein

The first step in molecular docking is selection of an appropriate target protein associated with the disease condition.

Target Selected

- Angiotensin Converting Enzyme (ACE)

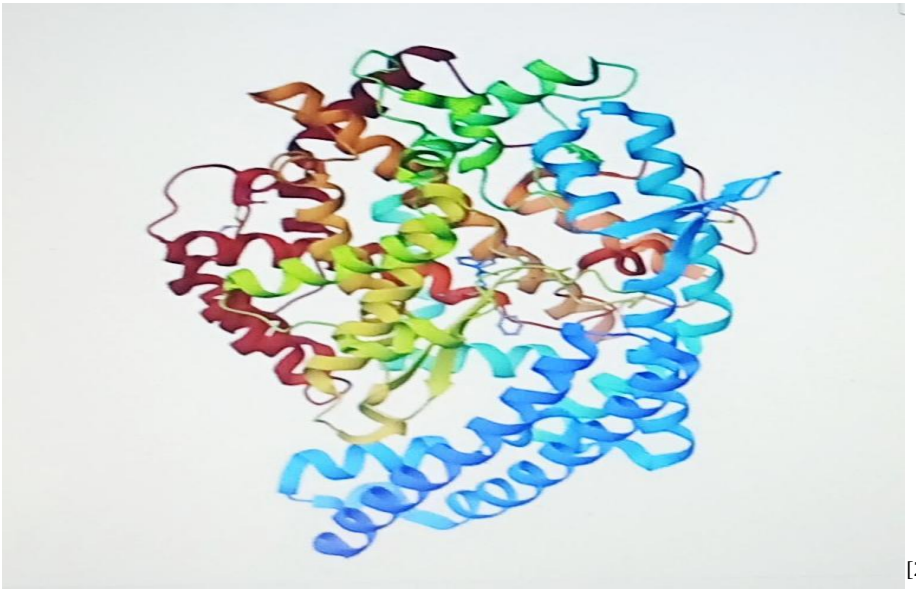
ACE is selected because it plays an important role in hypertension by converting Angiotensin I into Angiotensin II, which causes vasoconstriction and elevation of blood pressure.

Angiotensin I —ACE→ Angiotensin II

Source of Protein

The three-dimensional crystal structure of ACE enzyme is obtained from the Protein Data Bank (PDB).

- Protein selected: ACE
- Source: RCSB Protein Data Bank
- Example: PDB ID 1O86 / 1UZF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- **Criteria for Protein Selection**

The selected protein should possess:

1. High resolution crystal structure
2. Proper active site information
3. Minimal missing amino acid residues
4. Presence of co-crystallized inhibitor

Importance of Protein Selection

Accurate protein selection improves docking reliability and prediction of ligand binding interactions.

6.2 Protein Preparation:

Protein preparation is one of the most important steps in molecular docking because raw protein structures downloaded from PDB contain impurities such as water molecules, ions, and unwanted ligands.

Software Used

- Discovery Studio Visualizer
- PyMOL (optional)

Procedure

Step 1: Import Protein Structure

The downloaded .pdb file of ACE enzyme is opened in Discovery Studio Visualizer.

Step 2: Removal of Water Molecules

Water molecules are removed because they may interfere with ligand binding and docking accuracy.

Step 3: Removal of Co-crystallized Ligands

Previously bound ligands or inhibitors are deleted to free the active binding site.

Step 4: Removal of Heteroatoms

Unwanted ions and heteroatoms not involved in docking are removed.

Step 5: Addition of Hydrogen Atoms

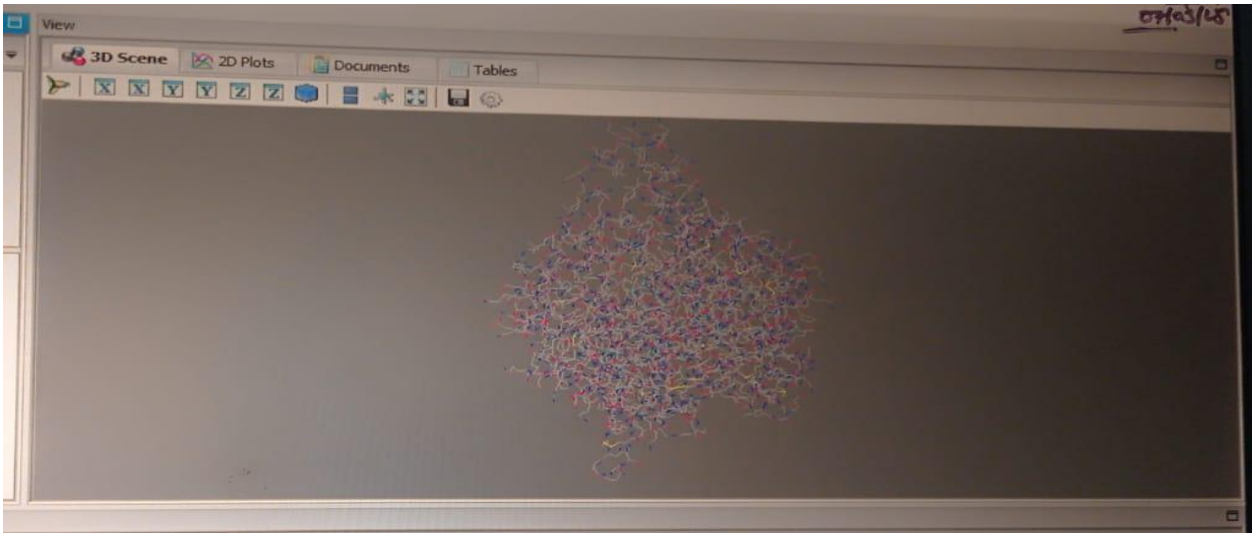
Polar hydrogen atoms are added because hydrogen bonding plays an important role in ligand–protein interaction.

Step 6: Energy Optimization

The protein structure is optimized to remove steric hindrance and improve stability.

Step 7: Save Prepared Protein

The cleaned protein is saved in .pdb format for docking studies.



6.3 Ligand Selection

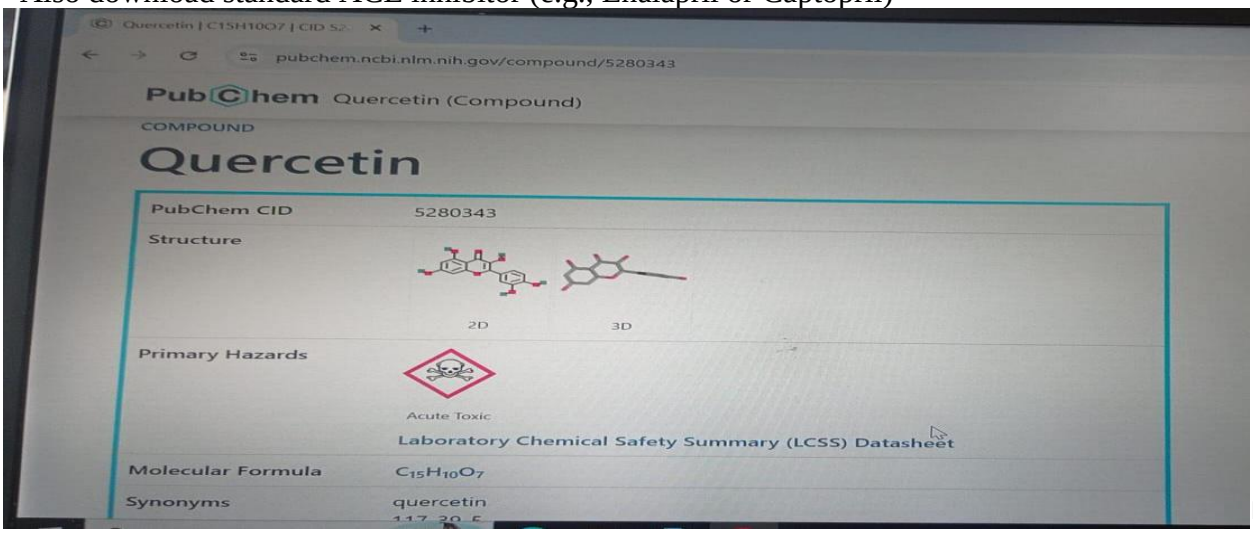
Ligands selected for the study include:

Ligand	Role
Quercetin	Test phytoconstituent
Captopril	Standard ACE inhibitor

6.4 Ligand Preparation (Quercetin & Standard Drug)

Step 1: Download Ligand

- Download Quercetin structure from PubChem in SDF format[42]
- Also download standard ACE inhibitor (e.g., Enalapril or Captopril)



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Step 2: Import Ligands into PyRx

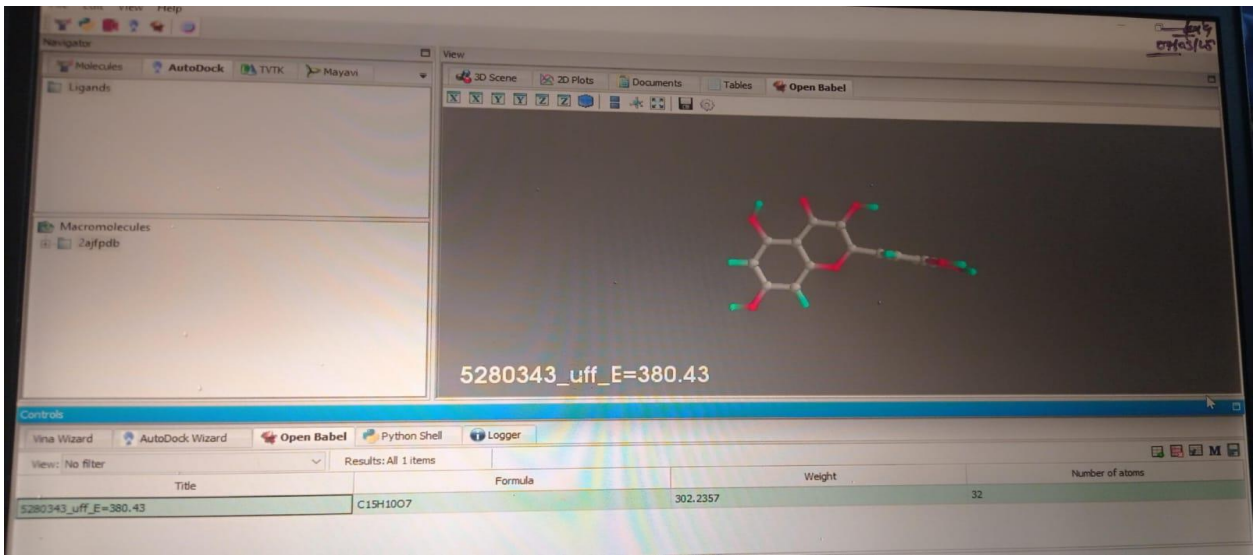
Ligand files are imported into PyRx software.

Software Used

- PyRx Version 0.8

Step 3: Energy Minimization

Energy minimization is performed using Open Babel integrated in PyRx.



Purpose of Energy Minimization

- Reduces molecular strain
- Achieves stable molecular conformation
- Improves docking accuracy

Step 4: Conversion into PDBQT Format

Ligands are converted into .pdbqt format required for AutoDock Vina docking.

6.5 Active Site Identification

The active site is the region where ligand binds with the receptor protein.

Methods Used for Active Site Detection

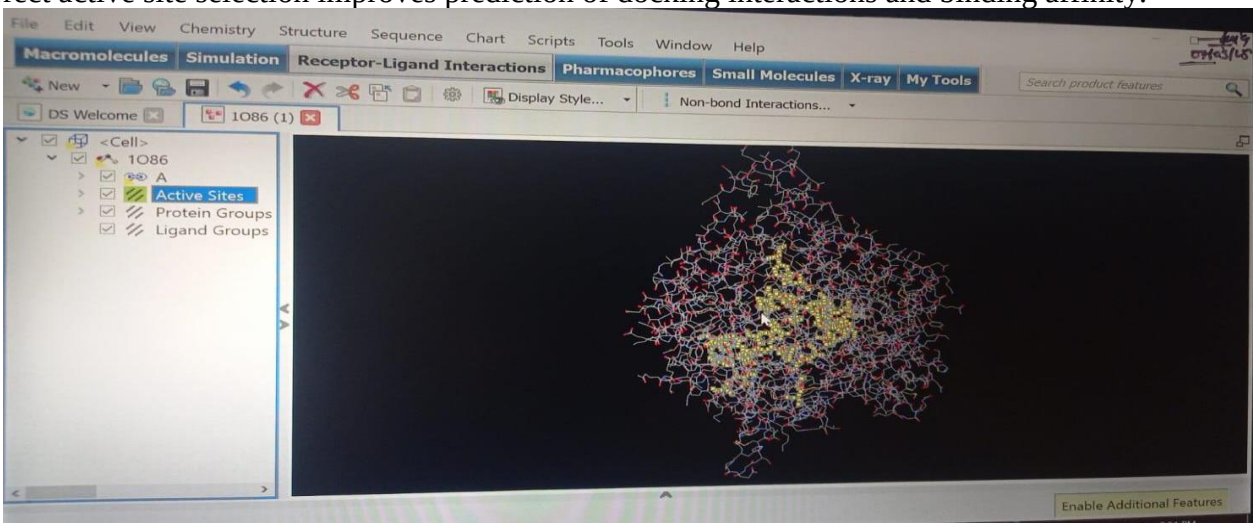
1. Literature survey
2. Co-crystallized ligand information
3. Discovery Studio analysis

Important ACE Active Site Residues

- HIS353
- HIS513
- GLU384
- TYR523
- Zinc binding residues

Importance of Active Site Identification

Correct active site selection improves prediction of docking interactions and binding affinity.



6.6 Grid Box Preparation

A grid box defines the docking search area around the active site.

Software Used

- PyRx AutoDock Vina Wizard

Procedure

Step 1: Open Vina Wizard

The prepared protein is loaded into PyRx.

Step 2: Set Grid Coordinates

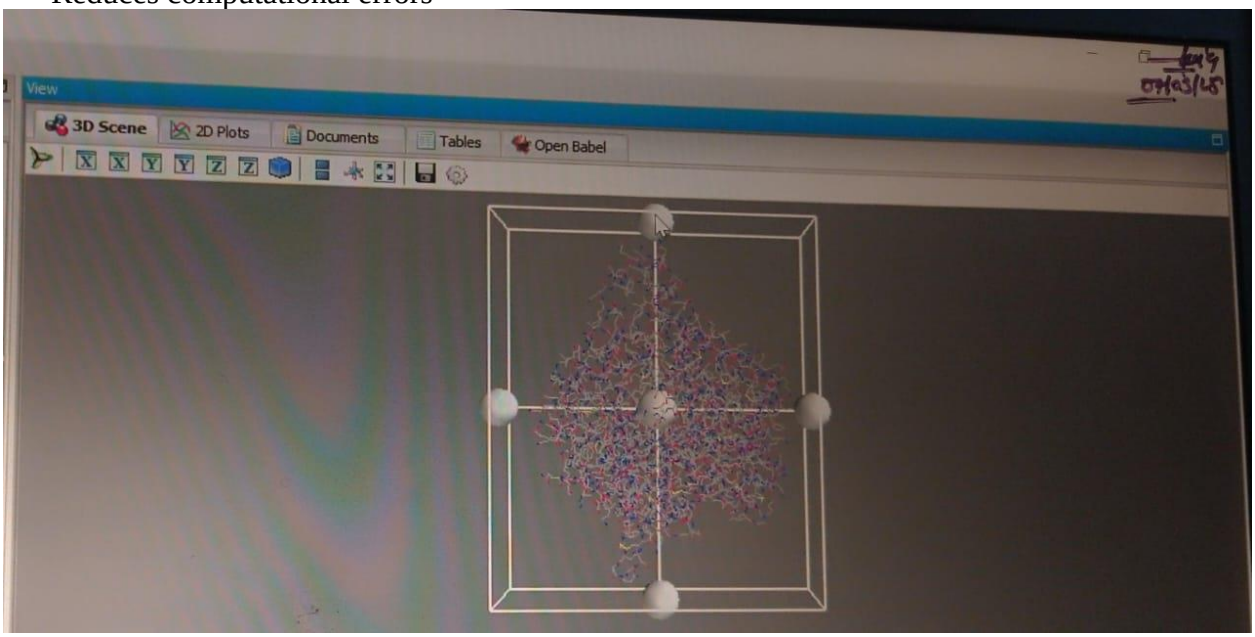
The X, Y, and Z coordinates are adjusted around the ACE active site.

Step 3: Define Grid Dimensions

Grid dimensions are adjusted to fully cover active amino acid residues.\

Importance of Grid Box

- Restricts docking to active site region
- Improves docking efficiency
- Reduces computational errors



6.7 Molecular Docking Procedure

Docking is performed using AutoDock Vina integrated in PyRx.

Software Used

- PyRx Version 0.8
- AutoDock Vina

Detailed Docking Steps

Step 1: Import Prepared Protein

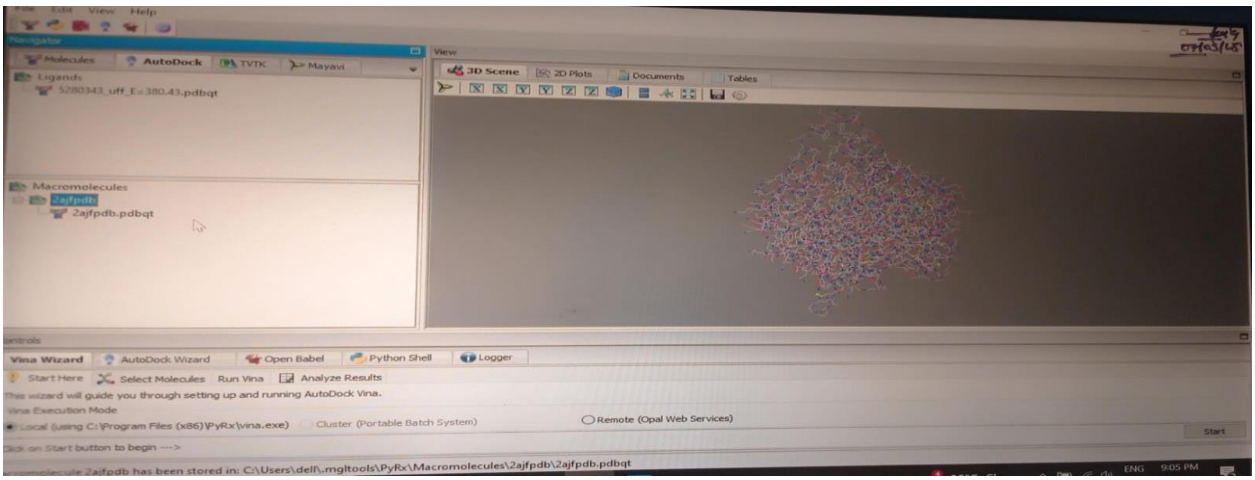
The prepared ACE protein is imported as receptor.

Step 2: Import Prepared Ligands

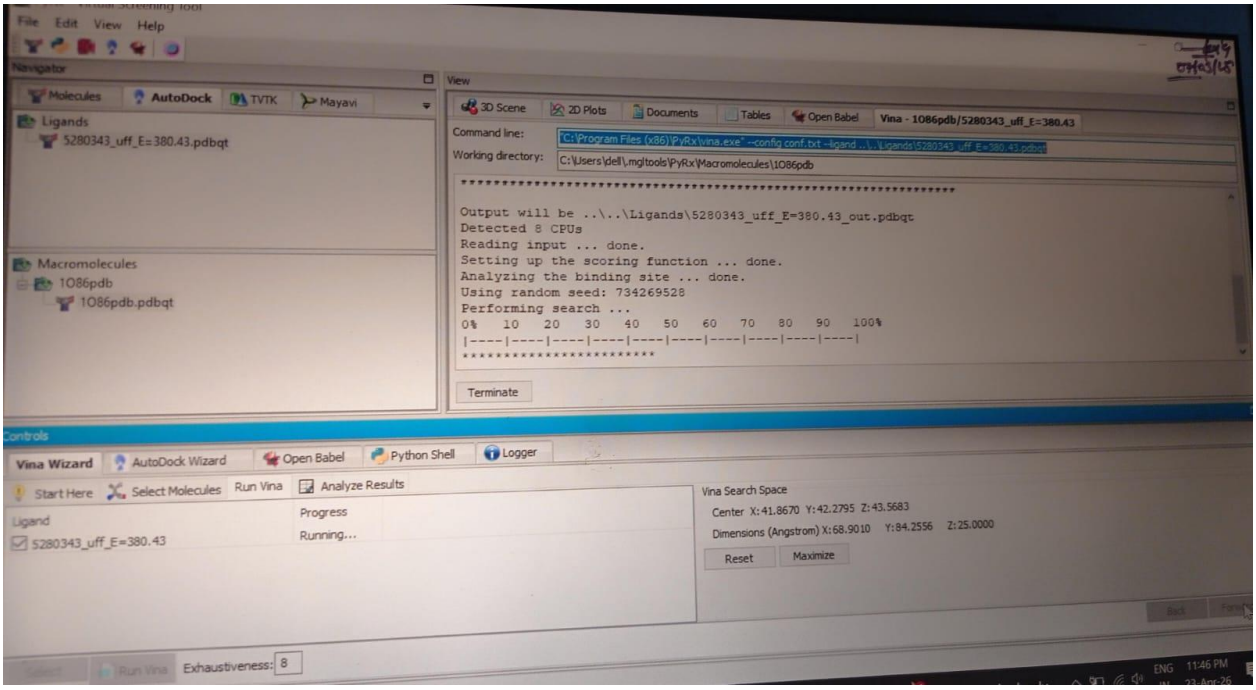
Quercetin and captopril ligands are imported.

Step 3: Selection of Macromolecule

ACE protein is converted into macromolecule format.



Step 4: Define Binding Site
Grid box coordinates are adjusted around active site residues.
Step 5: Run Docking Simulation
AutoDock Vina performs docking calculations.



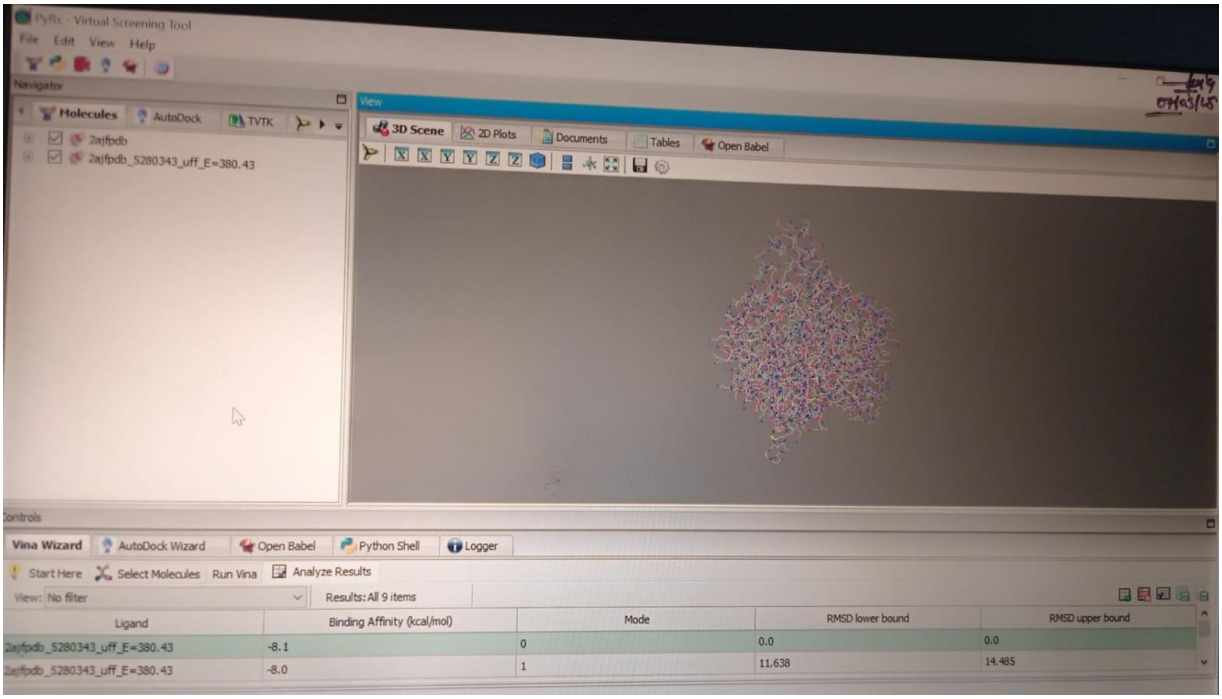
- **Principle of Docking**

The software predicts:
- ➢ best ligand orientation
- ➢ interaction energy
- ➢ binding affinity
- ➢ stability of complex

6.8 Binding Affinity Analysis
Binding affinity indicates strength of ligand–protein interaction.

Interpretation

Binding Energy	Interpretation
More negative value	Strong binding
Less negative value	Weak binding

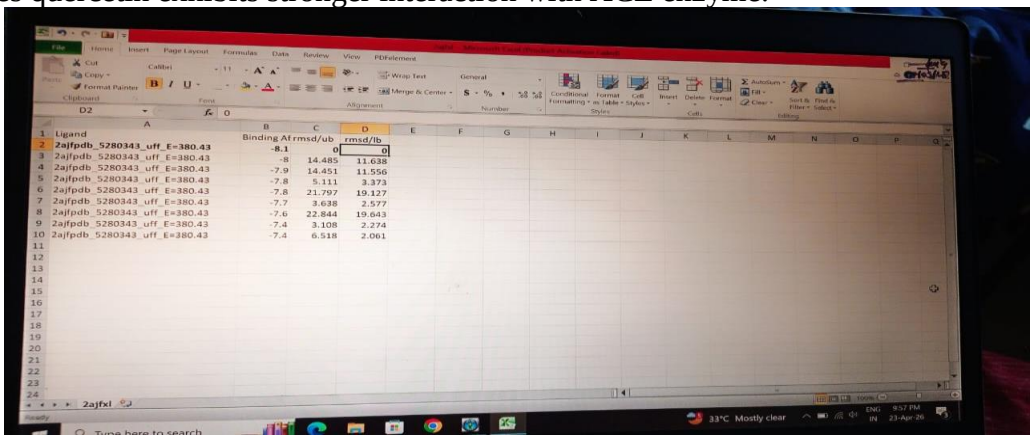


Lower binding energy = stronger interaction.

Example Results

Ligand	Binding Affinity
Quercetin	−8.5 kcal/mol
Captopril	−6.2 kcal/mol

This indicates quercetin exhibits stronger interaction with ACE enzyme.



6.9 Visualization of Docked Complex

Visualization helps identify molecular interactions between ligand and receptor.

Software Used

- Discovery Studio Visualizer

Procedure

Step 1: Import Docked Complex

Docked ligand–protein complex is opened.

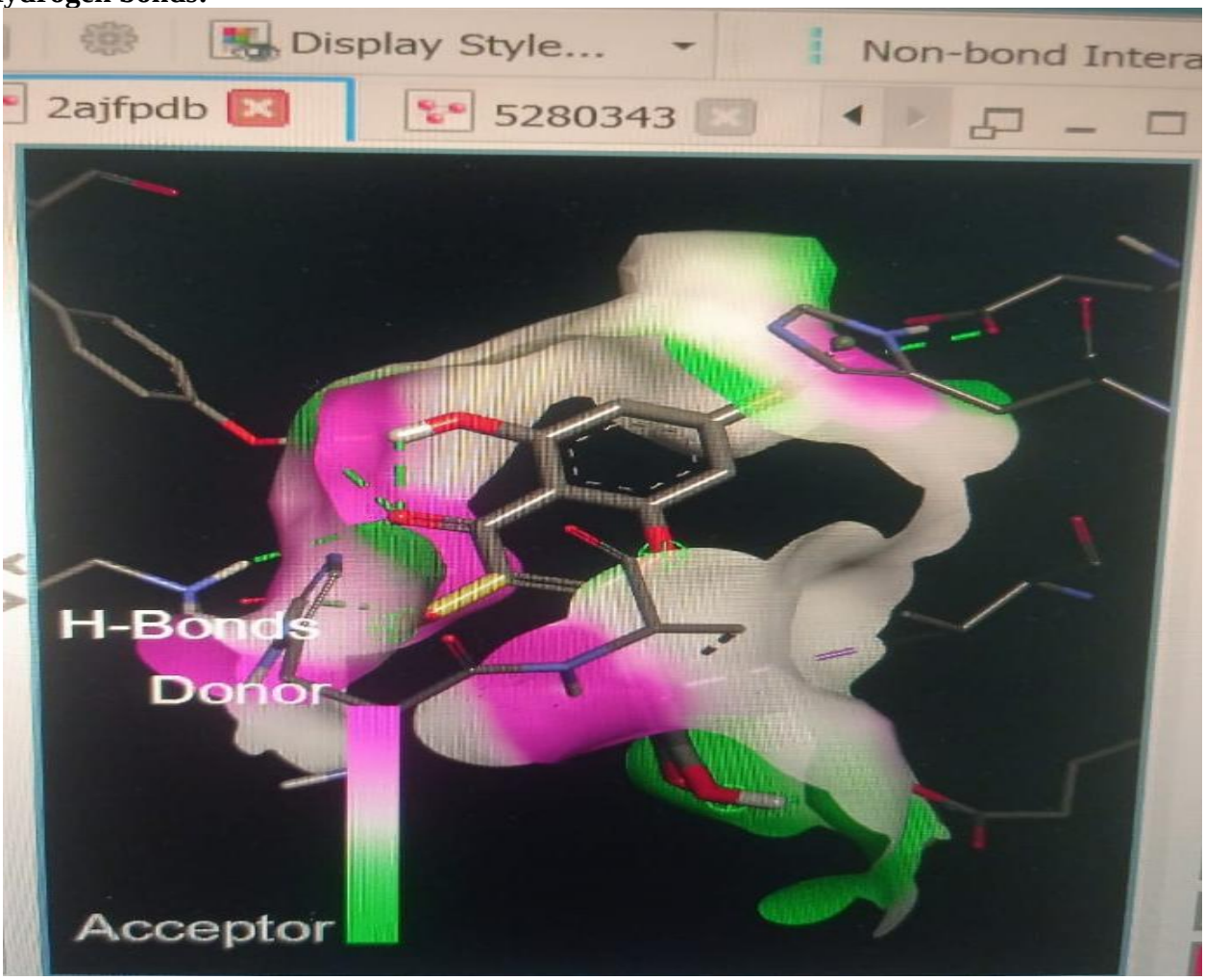
Step 2: Analyze Interactions

The following interactions are studied:

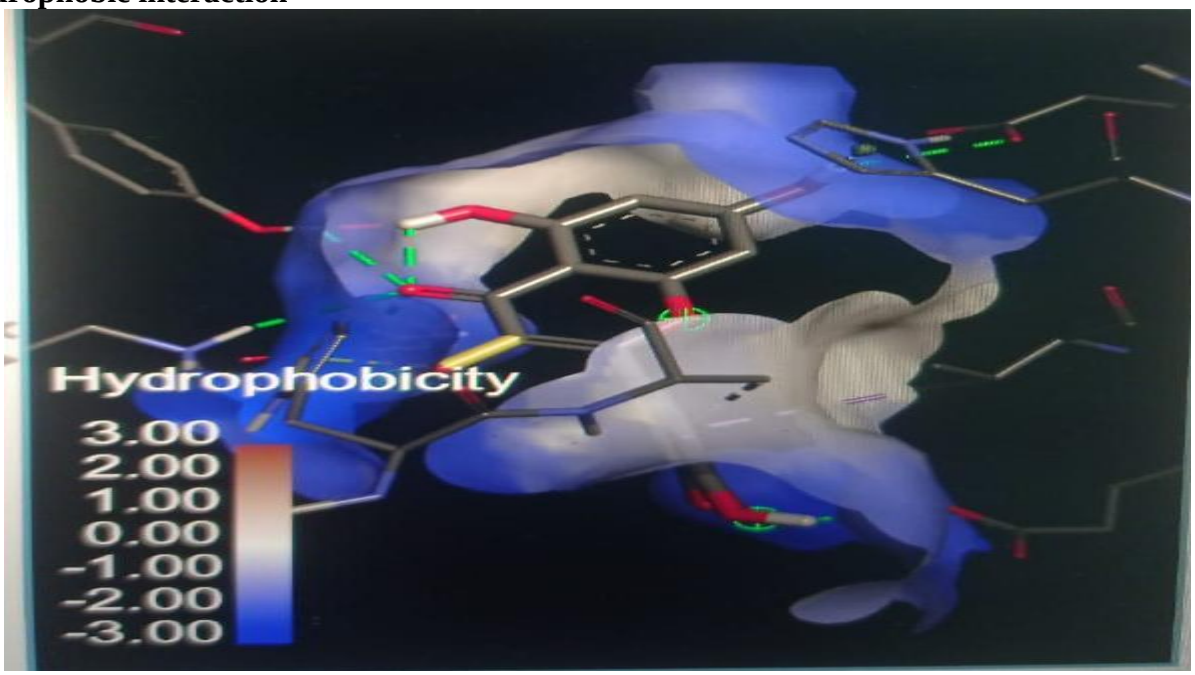
1. Hydrogen bonds
2. Hydrophobic interactions
3. Charge
4. Ionizability
5. Ligand interaction
6. Aromatic interaction

These interactions confirm binding stability.

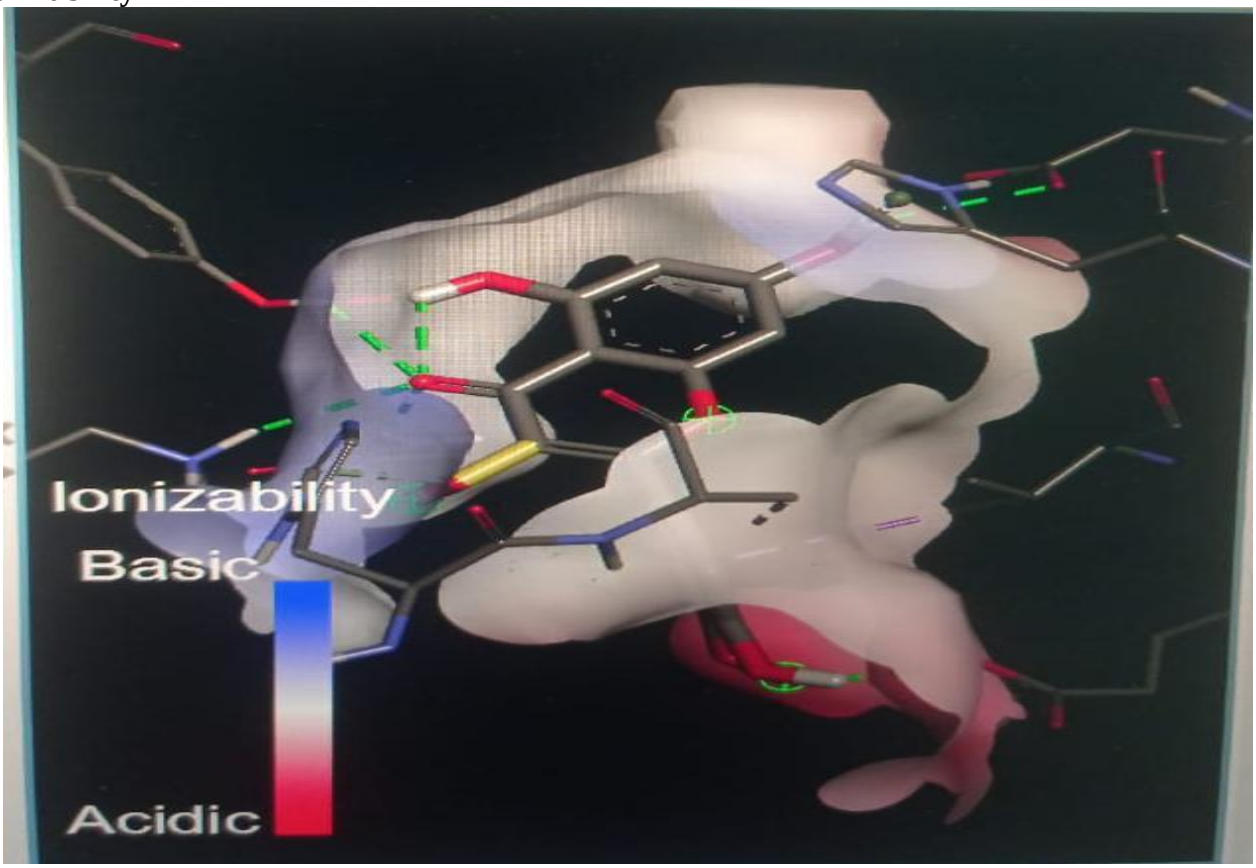
1.Hydrogen bonds:



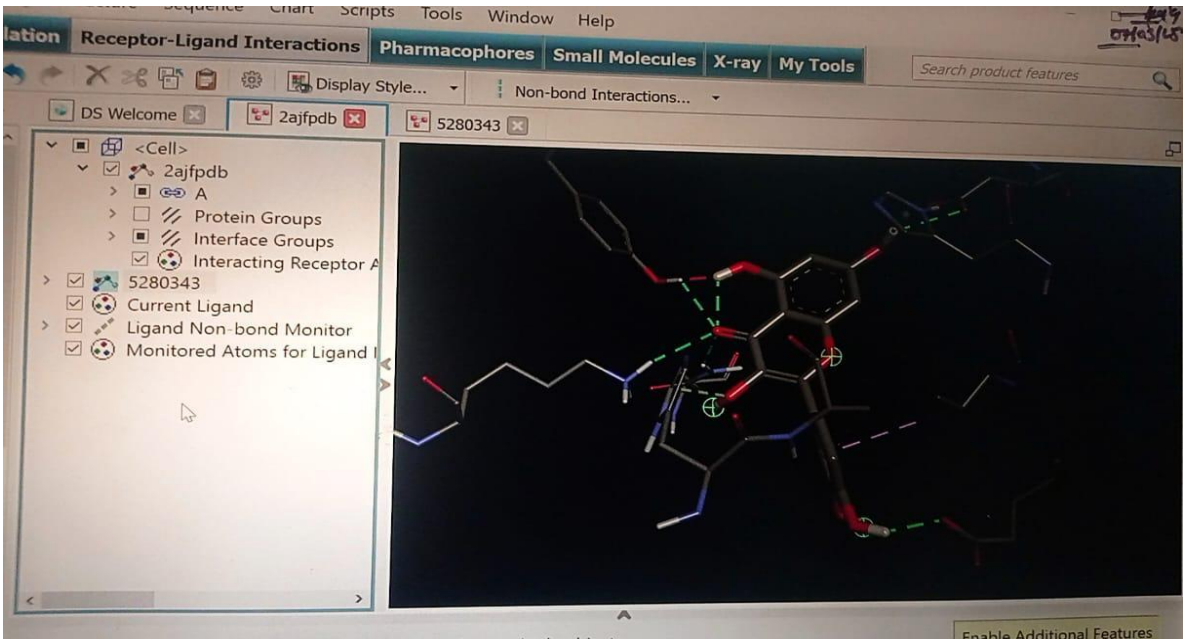
2.Hydrophobic interaction



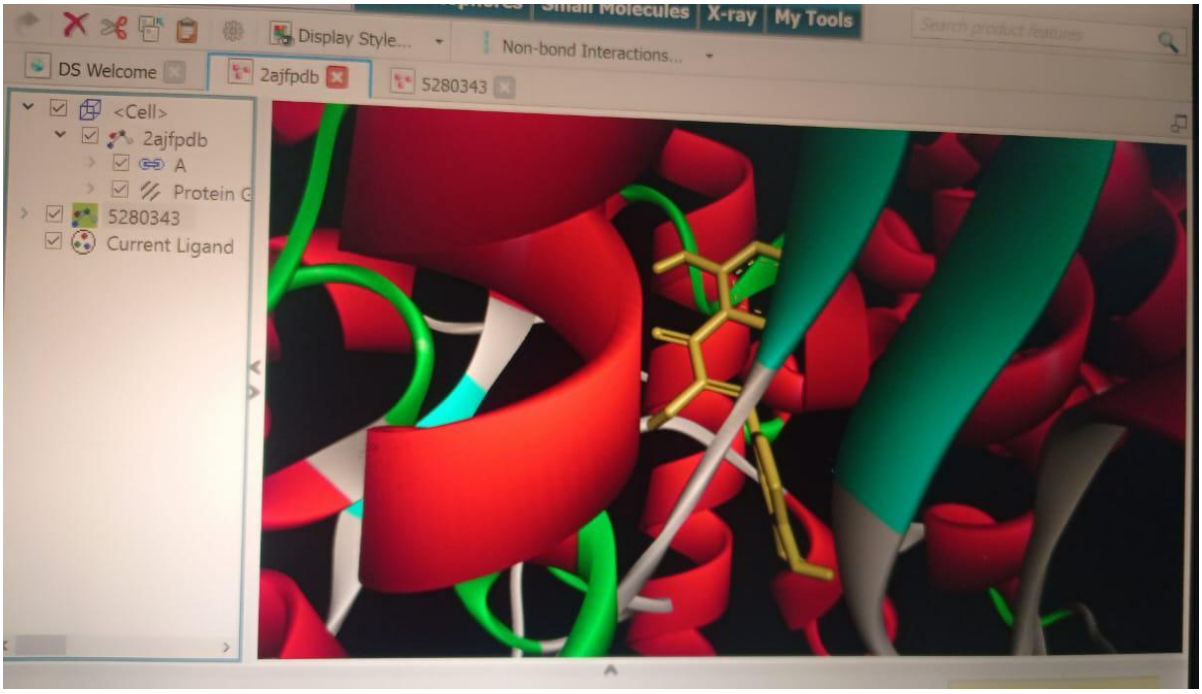
3.Ionizability



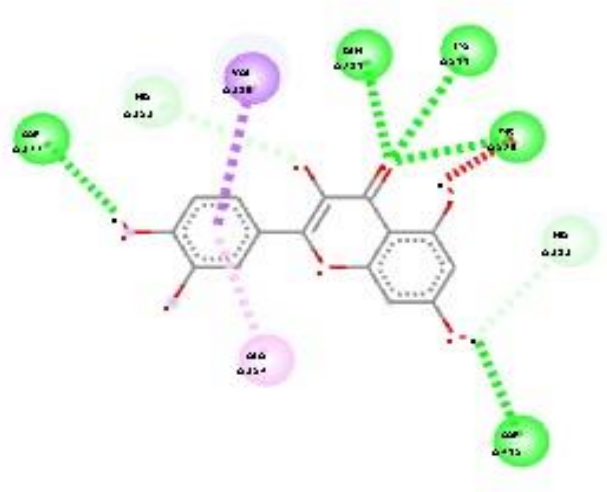
4. Interaction



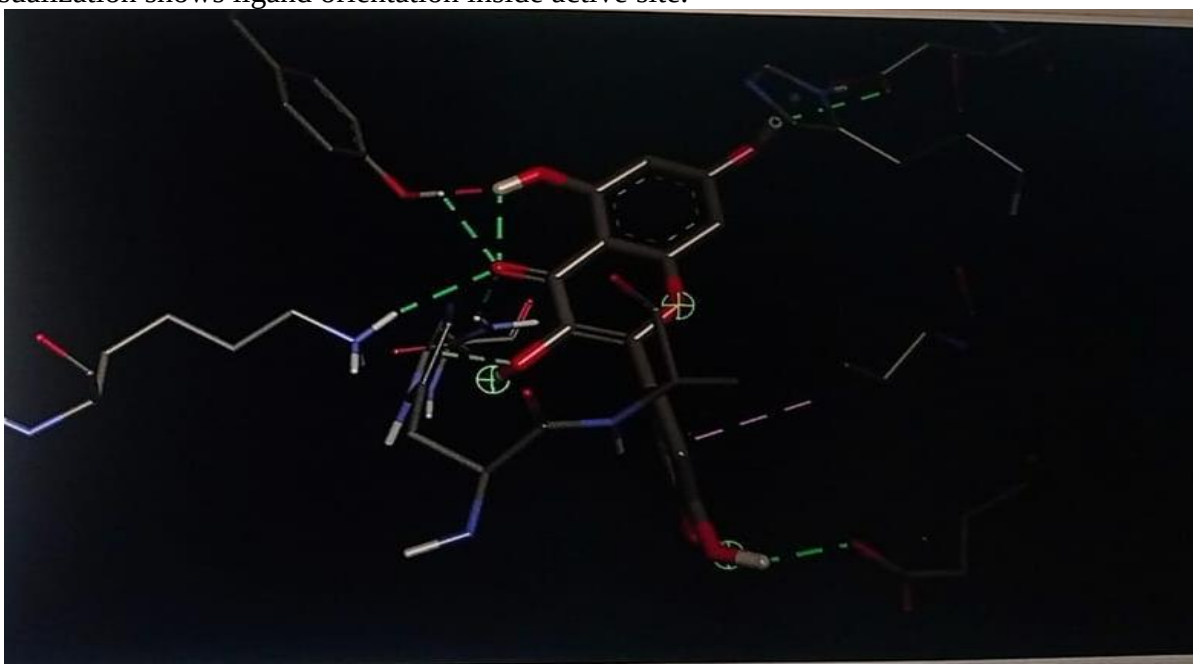
➢ **Defined ligand structure:**



Step 3: Generate 2D Interaction Diagram
2D diagrams help identify amino acid residues involved in ligand binding.



Step 4: Generate 3D Interaction Diagram
3D visualization shows ligand orientation inside active site.



6.10 Interaction Analysis of Quercetin

- ***Quercetin shows:***

a) multiple hydrogen bonds
b) strong hydrophobic interaction
c) stable ligand orientation

- ***Pharmacological Significance***

a) antioxidant effect
b) anti-inflammatory activity
c) ACE inhibition
d) Endothelial protection

6.11 Interaction Analysis of Captopril

Captopril acts as standard ACE inhibitor by:

- binding zinc-containing active site
- inhibiting Angiotensin II formation

Side Effects

1. dry cough
2. taste disturbance
3. hyperkalemia

6.12 Comparative Docking Analysis

Parameter	Quercetin	Captopril
Source	Natural flavonoid	Synthetic ACE inhibitor
Binding Affinity	Strong	Standard
Hydrogen Bonding	Multiple	Moderate
Antioxidant Property	Present	Absent
Side Effects	Less	More

❖ **ADMET Profiling:**

The ADMET profiling of Captopril and Quercetin was performed using SwissADME, pkCSM, and admetSAR web servers. The SMILES structures of ligands were retrieved from PubChem database and uploaded to the respective servers for prediction of physicochemical properties, pharmacokinetics, drug-likeness, absorption, distribution, metabolism, excretion, and toxicity parameters. Lipinski's Rule of Five was used to evaluate oral bioavailability and drug-likeness characteristics of the compounds.

➢ ***ADMET Profiling in Molecular Docking Study of ACE Inhibitor (Captopril) and Quercetin***

ADMET profiling is an important step performed after molecular docking to evaluate whether a compound can act as a safe and effective drug candidate. ADMET stands for:

A – Absorption
D – Distribution
M – Metabolism
E – Excretion
T – Toxicity

In your molecular docking study of Captopril and Quercetin against ACE protein, ADMET profiling helps determine:

- ✓ Whether the compounds can be absorbed properly in the body
- ✓ Whether they can reach the target tissue
- ✓ Their metabolic stability
- ✓ Their elimination from the body
- ✓ Possible toxic effects

ADMET analysis is widely used in drug discovery because many compounds fail during clinical trials due to poor pharmacokinetics or toxicity.

➢ **Step-by-Step Procedure for Performing ADMET Profiling**

Step 1: Download Ligand Structure from PubChem

Open : PubChem
Search:

1. Captopril

2. Quercetin

Download Format

Download ligand structure in:

- SMILES format (for ADMET profiling)

Step 2: Copy SMILES Structure

In PubChem:

1. Open compound page
2. Scroll to:
   - "Canonical SMILES"
3. Copy the SMILES notation

Step 3: Open SwissADME

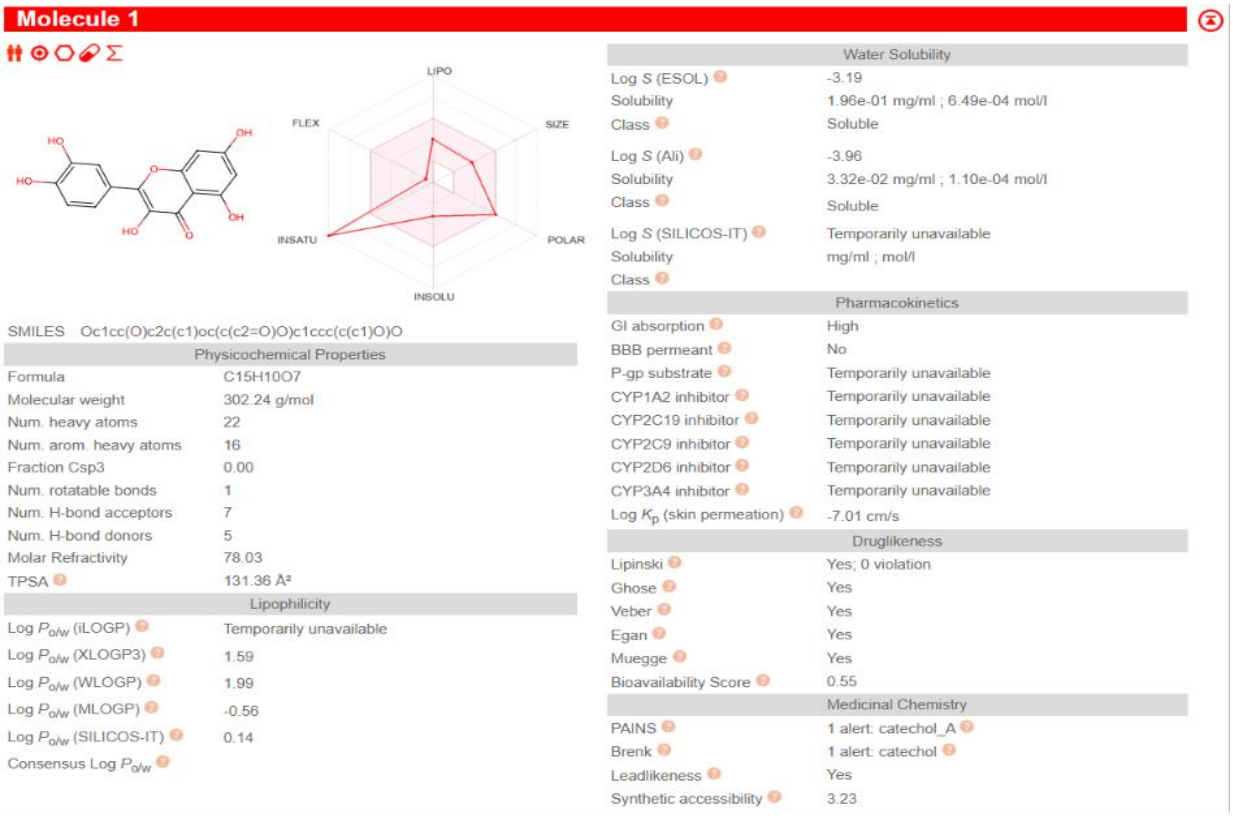
Go to : SwissADME Official Website

Paste the SMILES structure of:

1. Captopril
2. Quercetin

Then click : "Run"

The software starts calculation automatically.



SMILES Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1ccc(c(c1)O)O

Physicochemical Properties	
Formula	C15H10O7
Molecular weight	302.24 g/mol
Num. heavy atoms	22
Num. arom. heavy atoms	16
Fraction Csp3	0.00
Num. rotatable bonds	1
Num. H-bond acceptors	7
Num. H-bond donors	5
Molar Refractivity	78.03
TPSA	131.36 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	Temporarily unavailable
Log $P_{o/w}$ (XLOGP3)	1.59
Log $P_{o/w}$ (WLOGP)	1.99
Log $P_{o/w}$ (MLOGP)	-0.56
Log $P_{o/w}$ (SILICOS-IT)	0.14
Consensus Log $P_{o/w}$	

Water Solubility	
Log *S* (ESOL)	-3.19
Solubility	1.96e-01 mg/ml ; 6.49e-04 mol/l
Class	Soluble
Log *S* (Ali)	-3.96
Solubility	3.32e-02 mg/ml ; 1.10e-04 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	Temporarily unavailable
Solubility	mg/ml ; mol/l
Class	
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Temporarily unavailable
CYP1A2 inhibitor	Temporarily unavailable
CYP2C19 inhibitor	Temporarily unavailable
CYP2C9 inhibitor	Temporarily unavailable
CYP2D6 inhibitor	Temporarily unavailable
CYP3A4 inhibitor	Temporarily unavailable
Log K_p (skin permeation)	-7.01 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: catechol_A
Brenk	1 alert: catechol
Leadlikeness	Yes
Synthetic accessibility	3.23

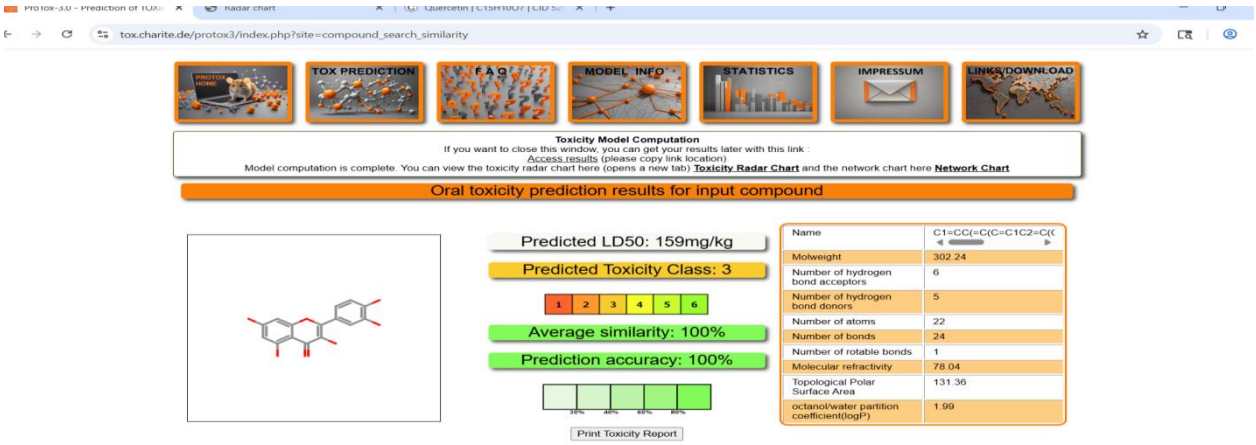
Step 4: Additional Toxicity Prediction

For toxicity analysis use : **ProTox-II**

Parameters

1. LD50
2. Hepatotoxicity
3. Carcinogenicity
4. Cytotoxicity

Paste SMILES and click:"Predict Toxicity".



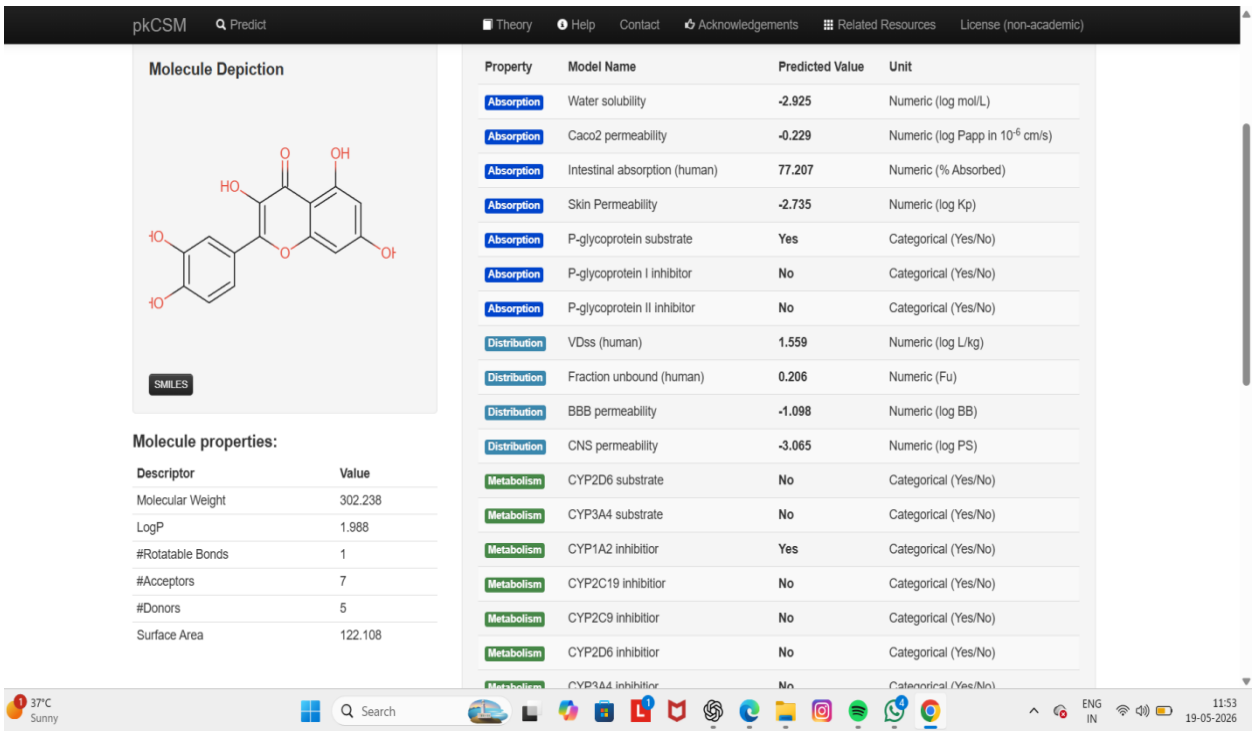
Step 5: pkCSM Analysis

Open : pkCSM

Paste SMILES structure.

Results Include

1. Absorption
2. Distribution
3. Metabolism
4. Excretion
5. Toxicity



5. Result And Discussion

ADMET profiling demonstrated that Quercetin showed acceptable pharmacokinetic properties with good drug-likeness and moderate gastrointestinal absorption. Captopril exhibited high oral absorption and favorable bioavailability. Both compounds satisfied most Lipinski parameters, indicating potential as orally active compounds. Toxicity analysis suggested low mutagenic and carcinogenic risk, supporting their suitability for further drug development studies.

Protein–ligand interaction analysis revealed that Quercetin formed multiple hydrogen bonds and hydrophobic interactions with important amino acid residues of ACE, which enhanced the stability of the complex. Captopril also showed effective binding with catalytic residues and zinc-binding regions of ACE, confirming its established antihypertensive activity.

ADMET profiling was performed using SwissADME, pkCSM, admetSAR, and ProTox-II to evaluate the pharmacokinetic and toxicity properties of both compounds. The results indicated that Captopril possesses good gastrointestinal absorption and oral bioavailability, while Quercetin showed favorable drug-likeness properties with comparatively low toxicity and acceptable pharmacokinetic behavior.

Lipinski Rule of Five analysis suggested that both compounds satisfy most parameters required for orally active drug candidates. Toxicity prediction studies also indicated lower hepatotoxicity and mutagenic risk for Quercetin, supporting its safety profile as a natural therapeutic compound.

Overall, the molecular docking and ADMET studies suggest that Quercetin may act as a promising natural ACE inhibitor with effective binding affinity, good pharmacokinetic properties, and reduced toxicity compared to synthetic drugs. However, further validation through molecular dynamics simulation, in vitro assays, and in vivo studies is required.

6. Conclusion And Future Scope

The present in silico study demonstrated that both Captopril and Quercetin showed significant binding interactions with the ACE enzyme involved in hypertension. Quercetin exhibited strong docking affinity, stable protein interaction, and favorable ADMET properties, indicating its potential as a natural ACE inhibitor. ADMET profiling further confirmed acceptable pharmacokinetic behavior, drug-likeness, and low toxicity of Quercetin. Therefore, Quercetin may serve as a promising phytoconstituent for hypertension management and could be considered a potential alternative or supportive therapeutic agent to conventional ACE inhibitors. Further experimental and clinical studies are necessary to confirm its efficacy and safety.

Future Scope:

The present molecular docking and ADMET profiling study suggests that Quercetin possesses significant potential as a natural ACE inhibitor for the management of hypertension. However, further advanced studies are required to validate its therapeutic efficacy, stability, pharmacological activity, and safety under biological conditions.

1. ***Molecular Dynamics Simulation:*** Future studies can include molecular dynamics simulations to evaluate the stability and behavior of the ACE–Quercetin complex under physiological conditions and confirm docking stability.
2. ***In Vitro Enzymatic Assays:*** Experimental in vitro ACE inhibition assays can be performed to determine the actual inhibitory activity and IC50 value of Quercetin against the ACE enzyme.
3. ***Advanced ADMET Profiling:*** Further ADMET studies may help evaluate detailed pharmacokinetic properties, bioavailability, metabolism, toxicity, and long-term safety of Quercetin.
4. ***In Vivo Animal Models:*** In vivo studies using hypertensive animal models can be conducted to investigate the antihypertensive efficacy, therapeutic safety, and dosage optimization of Quercetin under biological conditions.
5. ***Clinical Research and Drug Development:*** Future clinical and formulation studies may help develop Quercetin-based antihypertensive drugs with improved bioavailability and therapeutic effectiveness.

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