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DRUG LIKENESS PROPERTIES OF PHYTOCONSTITUENTS OF PSIDIUM GUAJAVA (GUAVA) AND THEIR MOLECULAR DOCKING AGAINST MONKEY POX VIRUS

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Abstract: Monkeypox is a worrisome new epidemic. The disease is caused by the monkeypox virus and is becoming more common worldwide, with an outbreak in 2022 spreading to Europe as part of the COVID -19 pandemic. The new outbreak is associated with new, previously undetected mutations and variants. In this study, virtual screening and molecular dynamics of secondary metabolites of Psidium guajava (guava) were used. Several compounds were predicted to bind tightly to viral proteins critical for viral replication, including molecules with high potential to bind thymidylate kinase and cysteine protease proteins, whose inhibition has been shown to suppress viral replication.

By molecular docking, the compounds kampferol, myricetin, chlorogenic acid, and quercetin were found to have considerable binding to these two receptors.

KEYWORDS:

Molecular docking, Monkeypox, Psidium Guajava

INTRODUCTION:

The re-emergence of various zoonotic diseases in humans by different species is a well-described phenomenon. Several outbreaks of zoonotic diseases have been reported in the 21st century. Factors such as climate change, animal husbandry, wildlife, and contact with humans have been implicated in disease outbreak. Zoonotic infections caused several diseases, and increased mortality rates were reported for infections such as Marburg virus and Ebola. The global health impact of these diseases and their social, economic, and psychological negative consequences are reported. Infectious disease outbreaks are associated with fear, anxiety, and uncertainty, and unconfirmed information circulates.

The widespread outbreak of monkeypox in 2022 is a typical example of the emergence and re-emergence of zoonotic monkeypox disease. After the initial reports of the monkeypox outbreak in the first quarter of 2022, local beliefs, rumours, fears, and unscientific views spread. Therefore, continued analysis of the prevalence of monkeypox disease and the extent of conspiratorial beliefs toward emerging viral infections-including monkeypox disease-is extremely useful from a pathological perspective. Monkeypox virus disease is a zoonotic disease and was considered endemic in Central and West Africa for about 50 years, with rare occasional outbreaks in the United States and Europe. Monkeypox virus is a DNA virus and is classified as an orthopox virus and has been grouped with the variola virus type. Variola virus is a causative agent of smallpox virus, and the structure of variola virus and monkeypox virus share structural features. These two viruses cause similar clinical symptoms. Both monkeypox virus and variola virus cause almost similar clinical symptoms on the skin. Smallpox vaccination provides cross-protection against monkeypox virus disease, and 85% protection has been reported. Treatment of monkeypox virus disease is based on daily care, and certain medications used to treat variola virus disease can also be used to treat monkeypox virus disease. Antibiotics are not usually used to treat monkeypox viral disease, but may be used to treat and prevent bacterial superinfection. In certain Middle Eastern countries, including Saudi Arabia, administration of vaccine immunoglobulin is recommended for treatment of monkeypox disease. Antiviral agents such as cidofovir and tecovirimat are recommended for the treatment of monkeypox virus in high-risk patients. Computational approaches are widely used in drug discovery and have become an integral part of drug screening programs. They allow screening of different small molecule libraries to identify lead molecules that can be optimized to develop a new lead molecule. In this study, potential phytoconstituents of Psidium guajava were used to screen against monkeypox virus.

Objectives

Monkeypox virus can vary depending on the specific research goals. However, here are some general objectives that could be pursued :

1. To study the drug likeliness properties of phytoconstituents of Psidium guajava
2. Identification of potential antiviral compounds -

   Molecular docking can aid in the screening and identification of specific phytoconstituents from Psidium Guasave that have the potential to interact with monkeypox virus target proteins/enzymes. By predicting binding affinities and interactions between the phytoconstituents. Ang viral proteins.
3. Understanding molecular interactions -

   Docking studies may provide insights into the molecular interactions between Psidium guajava phytoconstituents and viral proteins.

   By studying the binding modes and the specific amino acid residues involved in the interaction, we can gain a better understanding of the mechanism of action.
4. Virtual screening –

   Molecular docking can be used as a virtual screening tool to assess a large number of phytoconstituents from Psidium guajava and prioritize the most promising candidates for further experimental evaluation.

   It's important to note that molecular docking is a computational method used for in silico analysis and the findings should be validated through experimental studies to confirm the activity and efficacy of the identified phytoconstituents against monkeypox virus

Literature survey

Monkeypox virus

Monkeypox virus belongs to the orthopoxvirus group, which also includes smallpox, cowpox, vaccinia, and variola, and is endemic to West and Central Africa.

To date, infections have been reported primarily in central Africa, with the first case diagnosed in the Democratic Republic of Congo (DRC) in 1970. A review by Bunge et al. (2022) found that mortality rates varied between monkeypox strains in Africa from 3.6% to 10.6%, suggesting an increasing potential for fatal outcomes. Recent cases of monkeypox have been detected exported by travellers to Singapore, the United Kingdom, Israel, and the United States. An outbreak in the Midwestern United States in 2003 was associated with contact of prairie dogs with infected rodents from Ghana. No deaths due to monkeypox were reported in any of these outbreaks, but the number of reported cases ranged from a single case in Singapore, the United Kingdom, and Israel to 71 cases in the United States in the 2003 outbreak.

Monkeypox is transmitted through an animal bite or direct contact with an animal's body fluids. The disease can also be transmitted by respiratory droplet infection during direct and/or prolonged face-to-face contact, by direct contact with body fluids of an infected person, or by objects contaminated with virus particles . In the current outbreak, monkeypox is being discussed as a sexually transmitted disease (STD). Prevention of monkeypox is 85% effective with the smallpox vaccine.

Symptoms of monkeypox manifest as fever between 38.5°C and 40.5°C, malaise, and skin rash. The monkeypox incubation period ranges from 7 to 17 days, with fever resolving three days after the onset of the rash. The lesions are felt as swollen, stiff, and painful. Lymphadenopathy, which occurs in monkeypox but not in smallpox, is thought to cause a stronger immune response compared with smallpox. Following the lesion, scabs form and eventually fall off, resulting in discoloured patches. Cases of sepsis due to lesions have been reported, but they are generally considered rare.

Monkeypox is diagnosed by PCR, culture, immunohistochemistry such as ELISA, or electron microscopy, depending on the availability of the tests.

Treatment of monkeypox is supportive

Potential treatments currently identified include tecovirimat, which is approved by US FDA for the treatment of smallpox. Cidofovir or Brin cidofovir have also been listed as potentially effective agents for the treatment of monkeypox, but their use has not been studied outside of experimental models. The use of other drugs has not been extensively studied, leaving a gap in knowledge for the treatment of monkeypox. The monkeypox genome is similar to that of smallpox, with a previous study showing 96.3% identity in the central regions encoding key enzymes and proteins. The monkeypox genome nomenclature follows universal nomenclature but differs in specific regions encoding virulence. Of all the Poxviridae, vaccinia is one of the best studied because it is used to vaccinate against other poxviruses and is a much less dangerous relative of smallpox. Monkeypox, smallpox, and vaccinia have genome sizes of approximately 197 kb, 186 kb, and 190 kb, respectively. All poxvirus genomes are composed of linear, double-stranded DNA.

For clarity, two poxvirus targets are examined in this work:

(a) Thymidylate kinase (2v54)

(b) DNA Polymerase (8hm0)

which have been suggested as useful targets in other studies and reviews.

(a) Thymidylate kinase (2v54)

It catalysis the phosphorylation of thymidine 5 – monophosphate (dTMP) to form thymidine 5 – diphosphate (dTDP) in presence of ATP and magnesium :

ATP + Thymidine 5-phosphate = ADP + Thymidine 5 – diphosphate.

Thymidine kinse is a enzyme 25 kd and is important in the dTT synthesis pathway for DNA synthesis. The function of dTMP Kinase in eukaryotic comes from study of the cell mutant, cdc8, in saccharomyces cerevisiae.

Structural and functional analysis suggest that cDNA codes for authentic human dTMP kinase. The mRNA level and enzyme activities corresponded to cell cycle progression and cell growth stages. (2)

(b) DNA Polymerase (8hm0)

DNA polymaerses catalyze templete dependent DNA synthesis during genome replication & repair. This enzyme is responsible for prefentially binding and incorporating in nucleotide, from pool of chemically and structurally similar molecules, that correctly base pairs with the appropriate templeting base.

Methodology

Molecular Docking

Molecular docking is a type of computational modelling that facilitates the prediction of the preferred binding orientation of one molecule (e.g., ligand) to another (e.g., receptor) when the two interact to form a stable complex. The information obtained from the preferred orientation of the bound molecules can be used to predict the energy profile (e.g., free energy of binding), strength, and stability (e.g., binding affinity and binding constant) of the complexes. This can be done using the scoring function of molecular docking. Nowadays, molecular docking is widely used to predict the binding orientation of small molecules (drug candidates) to their biomolecular target (e.g., proteins, carbohydrates, and nucleic acids) to determine their preliminary binding parameters. In this way, raw data are obtained for rational design (structure-based drug discovery) of new drugs with better efficacy and greater specificity. The main goal of molecular docking is to achieve an optimized docked conformer of the two interacting molecules to reduce the free energy of the whole system. The predicted final binding free energy (ΔGobind) is modelled in terms of dispersion and repulsion (ΔGvdw), hydrogen bonding (ΔGobind), desolation (ΔGdesolv), electrostatic energy (ΔGelled), torsional free energy (ΔGhor), final total internal energy (ΔTotal), and the energy of the unbound system (ΔGunb). Therefore, a detailed understanding of the general principles that govern the predicted free energy of binding (ΔGbind) provides additional information about the nature of the different types of interactions that govern the docking of molecules. The practical application of molecular docking requires a structural database to search for the desired target and a methodology to evaluate the ligand. To achieve this, several molecular docking tools and methods are available. These computational tools provide a hierarchy of potential ligands based on their ability to interact with specific targets.

Molecular docking of small molecules to a biological target involves an imaginative scanning of possible positions of the ligand in the specific groove or pocket of the target candidate to determine the optimal binding geometry. This can be done using a custom fitness or scoring function of the docking software.

This provides a surrogate approach for determining target structure, which is the starting point for in silico discovery of high affinity drug candidates. There are several databases that provide information on small ligand molecules, such as CSD (Cambridge Structural Database), ACD (Available Chemical Directory), MDDR (MDL Drug Data Report), and NCI (National Cancer Institute Database). In molecular docking, different docked conformers (poses) are generated, evaluated, and compared. One of the poses is either accepted or rejected based on the evaluation function of the docking software. In the case of rejection,

new poses are generated and the search procedure continues until the end point of acceptance of a pose. In molecular docking, the search and evaluation are closely linked. However, evaluating the docked conformers according to their experimental binding affinities and binding free energies seems to be more challenging than searching for their binding orientations. To overcome this challenge, different scoring functions are used, such as consensus scoring or applying multiple scoring functions to the same docked pose to avoid false positives.

Approaches to molecular docking Two main types of approaches are used to perform molecular docking. One of the approaches uses computer simulations in which the energy profile for the docked conformer of the ligand target is estimated. The second approach, on the other hand, uses a technique to calculate the surface complementarity between the ligand and the target. Both approaches are briefly described below, and their main features are also summarized in Table 1

Simulation approach - In this approach, the ligand and target molecules are separated by a certain physical distance, and then the ligand is allowed to bind into the groove/pocket of the target molecule after a certain number of movements in its conformational space. The motions involve changes in the ligand structure either internally (rotational angle rotations) or externally (rigid body transformations such as rotations and translations). Each movement within the conformational limits of the ligand generates energy, which is calculated as the “total energy of the system." This approach is more advantageous than shape complementarity because it is better suited to integrate ligand flexibility into the molecular modeling tool. Another advantage of this approach is that molecular recognition between ligand and target molecule can be evaluated more realistically.

Lipinski Rule

The restriction of ADME properties by the Lipinski rule: a molecular weight of less than 500 daltons, hydrogen bond donors of no more than 5, hydrogen bond acceptors of no more than 10, and an octanol-water partition coefficient log P of no more than 5. The swissadme software was used to test the selected ligands for their Lipinski rule. Swissadme aims to evaluate the pharmacokinetics and pharmacodynamics of the ligand by checking the drug properties. Key ADME properties (log P, H-binding donor, H-binding acceptor, and molecular weight) are predicted. Based on Lipinski’s rule in swissadme, the molecular properties and drug similarity of the phytochemical compounds were investigated.

Psidium Guajava

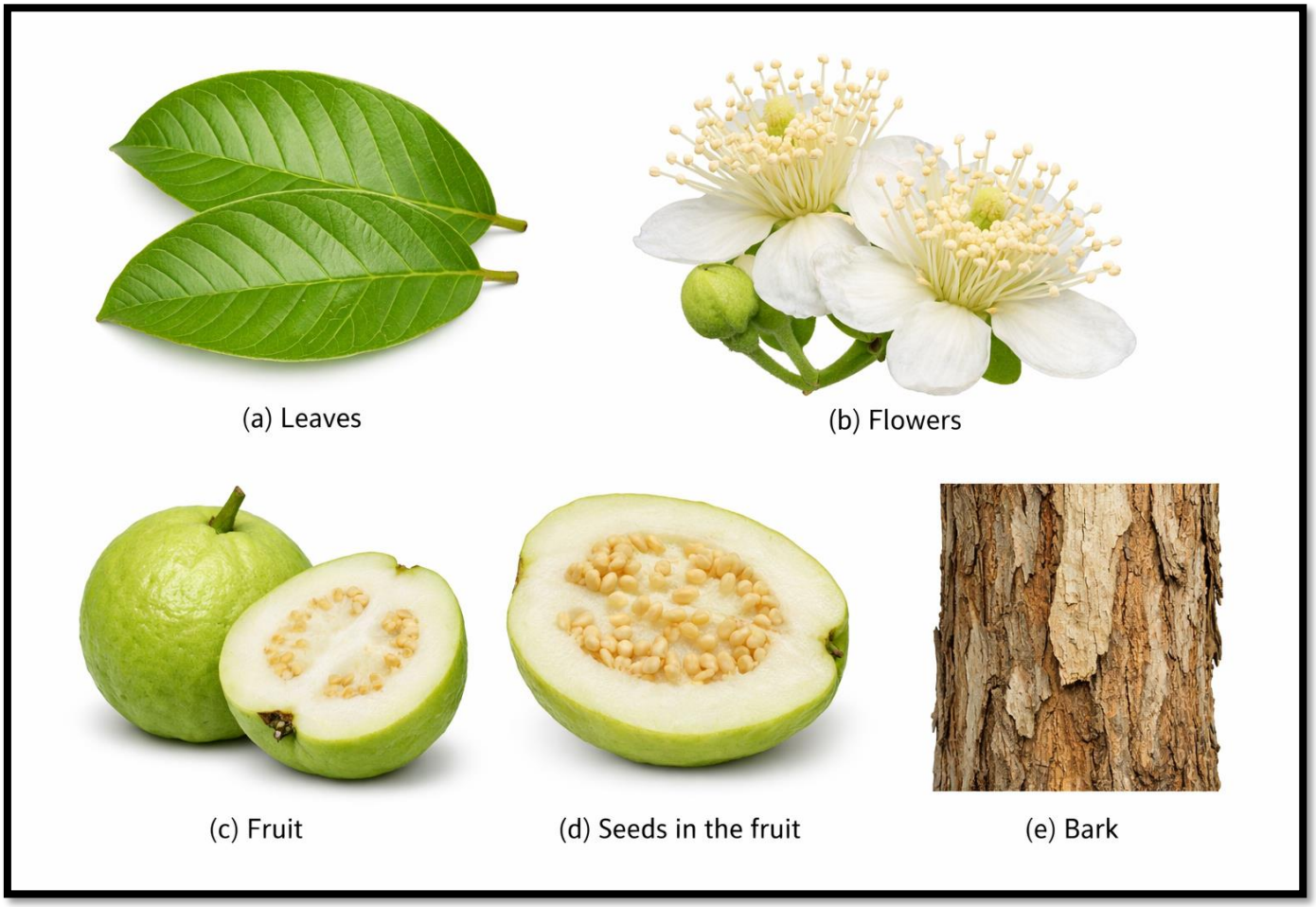
Psidium guajava (guava) is a well-known tropical tree that is widely cultivated for its fruit. In many countries, guava has long been used for medicinal purposes. This plant is used to treat diarrhea, dysentery, gastroenteritis, hypertension, diabetes, tooth decay, and pain relief, as well as to improve musculoskeletal coordination.

The extract from the leaves is used as a medicine for cough, diarrhea, mouth ulcers and swollen gums. The fruit is rich in vitamins A, C, iron, phosphorus, calcium and minerals. It contains high levels of organic and inorganic compounds such as secondary metabolites, e.g. antioxidants, polyphenols, antiviral compounds and anti-inflammatory compounds. The phenolic compounds in guava help heal cancer cells and prevent premature skin aging. The presence of terpenes, caryophyllene oxide and p-selinene causes a relaxing effect. Guava leaves contain many compounds that have fungistatic and bacteriostatic effects. Guava has high content of important antioxidants and possesses radioprotective effect. (4)

Guava has antiviral, anti-inflammatory, anti-plaque and antimutagenic properties

Background

- **Synonym** - Guava, Peru, Amrood
- **Kingdom** - Plante
- **Phylum** - Magnoliophyta / tracheohyta
- **Class** - Magnoliopsida
- **Order** - Myrtales
- **Family** - Myrtaceae
- **Species** - Psidiumguajava



Various parts of guava (a) Leaves (b) Flowers (c) Fruit (d) Seeds in the fruit (e) Bark

Plant Description

Psidium guajava is an evergreen shrubby tree that reaches a height of 6 to 25 feet. Figure 1 shows the various parts of the plant, i.e., leaves, flowers, fruits, seeds, and bark.

The plant has a widely branched network of branches. Mostly the branches are curved and bear opposite leaves with small petioles of 3 to 16 inches. The leaves are broad and clear green in color with distinct and prominent veins. The plant produces white flowers with curved petals that give off a pleasant fragrance. The flowers have four to six petals and yellow colored anthers, and pollination is by insects. The guava fruit is small to medium sized and 3 to 6 cm long. It has a pear-like shape and a yellow color when ripe. When ripe, it has a strong but pleasant musky odor. The flesh is slightly darker in color and contains slightly yellowish seeds. The size of the seeds is very small and they are easy to chew. They are arranged in regular

patterns; their number ranges from 112 to 535. The guava rind is thin and has green colored spots. It is very easy to peel off in long ribbons. It has a high content of antimicrobial and antibacterial compounds. Ethanolic extracts from the stem have high antidiabetic activity. Guava contains a large number of antioxidants and phytochemicals, including essential oils, polysaccharides, minerals, vitamins, enzymes, triterpenoid acid alkaloids, steroids, glycosides, tannins, flavonoids and saponins. Guava contains higher levels of vitamin C and vitamin A. Guava is also a very good source of pectin, an important dietary fiber. It has a high content of flavonoids, fructose sugars and carotenoids. Considering the historical background, important constituents and common use of Psidium guajava (guava), current studies are focused on the phytochemistry and medicinal value of this useful plant.

Chemical composition of guava

Guava fruit contains vitamin A, C, iron, phosphorus and calcium. It contains more vitamin C than the orange. The fruit contains saponin, oleanolic acid, lyxopyranoside, arabopyranoside, guaijavarin, quercetin and flavonoids. Ascorbic acid and citric acid are the major constituents of guava, which play an important role in antimutagenic activity.

Guava fruits contain terpenes, caryophyllene oxide and p-selinene in large quantity, which have relaxing effect. The content of flavonoids is higher in the methanolic extract of guava. There are 41 hydrocarbons, 25 esters, 13 alcohols and 9 aromatic compounds in guava.

Guaiaadial is also present in guava. The leaves contain essential oil containing α-pinene, limonene, β-pinene, isopropyl alcohol, menthol, terphenyl acetate, caryophyllene, longicyclene, and β-bisabolene. Oleanolic acid is also present in guava leaves. The leaves have a high content of limonene (about 42.1%) and caryophyllene (about 21.3%).

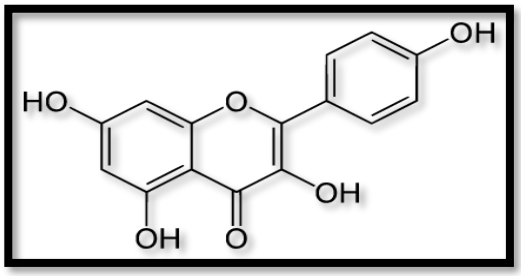
The leaves of guava contain many volatile compounds. The bark contains 12–30% tannin and one source states that it contains 27.4% tannin or polyphenols, resin and calcium oxalate crystals. Tannin is also present in the roots. Leucocyanidins, gallic acid, and sterols are also present in the roots. Carbohydrates and salts are present in large quantity. Tannic acid is also a part of it.(3)

Medicinal importance of guava

1. Psidium guajava L. is consumed in subtropical areas around the world not only as food but also as folk medicine for its pharmacological effects.
2. Medicinal plants occupy a very important place in the medical systems of almost the whole world. These observations are reflected in traditional knowledge.
3. It is known that guava is widely used in many parts of the world to cure many diseases such as diarrhea, fever, dysentery, gastroenteritis, hypertension, diabetes, tooth decay, pain relief and wounds.
4. Countries that have a long history of using medicinal plants also use guava extensively, such as Mexico, Africa, Asia and Central America.
5. In addition to its medicinal uses, guava is also used as a food and in food preparation.
6. It is also used in the construction of houses and in the manufacture of toys.
7. Guava contains high levels of organic and inorganic compounds such as secondary metabolites, e.g. antioxidants, polyphenols, antiviral compounds and anti-inflammatory compounds.
8. Guava contains a variety of compounds that have anti-cancer effects.
9. It contains a greater number of vitamins and minerals.
10. Phenolic compounds such as flavonoids also occupy an important place in guava.
11. Lycopene and flavonoids are important antioxidants. They help heal cancer cells and help prevent skin aging ahead of time.
12. Guava can affect heart muscle tension. Guava peel extract can control the degree of diabetes after 21 days

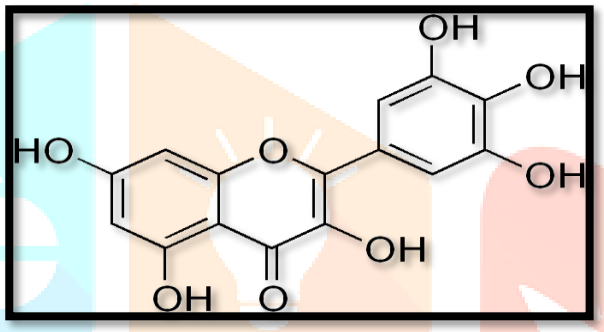
Drug Likeliness

Drug likeliness of selected constituents are given in following table:

KAEMPFEROL	
 SMILES Oc1ccc(cc1)c1oc2cc(O)cc(c2c(=O)c1O)O	
Physicochemical Properties	
Formula	C15H10O6
Molecular weight	286.24 g/mol
Num. heavy atoms	21
Num. arom. heavy atoms	16
Fraction Csp3	0.000
Num. rotatable bonds	1
Num. H-bond acceptors	6
Num. H-bond donors	4
Molar Refractivity	76.01
TPSA	111.13 Å²
LIPOPHILICITY	
Log P o/w (iLOGP)	1.70
Log P o/w (XLOGP3)	1.90
Log P o/w (WLOGP)	2.28
Log P o/w (MLOGP)	-0.03
Log P o/w (SILICOS-IT)	2.03
Consensus Log P o/w	1.58

WATER SOLUBILITY	
Log S (ESOL)	-3.31
Solubility	1.40e-01 mg/ml ; 4.90e-04 mol/l
Class	Soluble
Log S (Ali)	-3.86
Class	Soluble
Solubility	3.98e-02 mg/ml ; 1.39e-04 mol/l
Log S (SILICOS-IT)	-3.82
Solubility	4.29e-02 mg/ml ; 1.50e-04 mol/l
Class	Soluble
PHARMACOKINETICS	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K p (skin permeation)	-6.70cm/s
DRUGLIKENESS	
Lipinski	Yes,0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

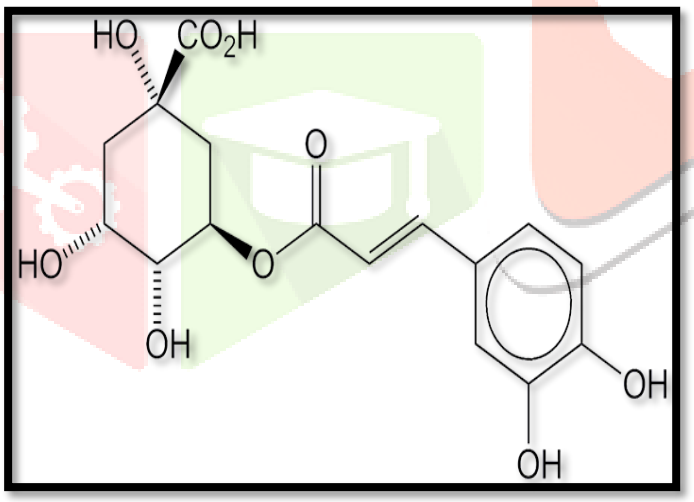
MEDICINAL CHEMISTRY	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	Yes
Synthetic accessibility	3.14

MYRECETIN	
 SMILES Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1cc(O)c(c(c1)O)O	
Physicochemical Properties	
Formula	$C_{15}H_{10}O_8$
Molecular weight	318.24 g/mol
Num. heavy atoms	23
Num. arom. heavy atoms	16
Fraction Csp3	0.00
Num. rotatable bonds	1
Num. H-bond acceptors	8
Num. H-bond donors	6
Molar Refractivity	80.06
TPSA	151.59 $Å^2$
LIPOPHILICITY	
Log P o/w (iLOGP)	1.08

Log P o/w (XLOGP3)	1.18
Log P o/w (WLOGP)	1.69
Log P o/w (MLOGP)	-1.08
Log P o/w (SILICOS-IT)	1.06
Consensus Log P o/w	0.79
WATER SOLUBILITY	
Log S (ESOL)	-3.01
Solubility	3.14e-01mg/ml ; 9.88e-04 mol/l
Class	Soluble
Log S (Ali)	-3.96
Solubility	3.50e-02 mg/ml ; 1.10e-04 mol/l
Class	Soluble
Log S (SILICOS-IT)	-2.66
Solubility	6.98e-01 mg/ml ; 2.19e-03 mol/l
Class	Soluble
PHARMACOKINETICS	
GI absorption	Low
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K p (skin permeation)	-7.40 cm/s
DRUGLIKENESS	
Lipinski	Yes; 1 violation: NH or OH>5

Ghose	Yes
Veber	No; 1 violation: TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 2 violations: TPSA>150, H-don>5
Bioavailability Score	0.55
MEDICINAL CHEMISTRY	
PAINS	1 alert: catechol_A
Brenk	1 alert: catechol
Leadlikeness	Yes
Synthetic accessibility	3.27

CHLOROGENIC ACID



SMILES O=C(OC1CC(O)(CC(C1O)O)C(=O)O)C=Cc1ccc(c(c1)O)O

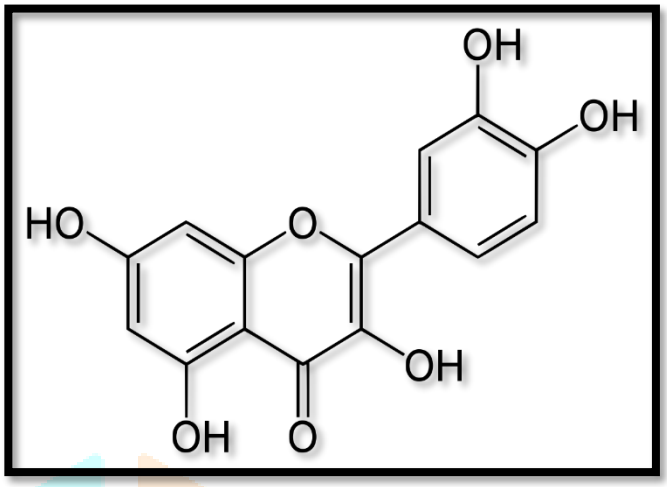
Physicochemical Properties

Formula	C16H18O9
Molecular weight	354.31 g/mol
Num. heavy atoms	25
Num. arom. heavy atoms	6
Fraction Csp3	0.38
Num. rotatable bonds	5

Num. H-bond acceptors	9
Num. H-bond donors	6
Molar Refractivity	83.50
TPSA	164.75 Å²
LIPOPHILICITY	
Log P o/w (iLOGP)	0.96
Log P o/w (XLOGP3)	-0.42
Log P o/w (WLOGP)	-0.75
Log P o/w (MLOGP)	-1.05
Log P o/w (SILICOS-IT)	-0.61
Consensus Log P o/w	-0.38
WATER SOLUBILITY	
Log S (ESOL)	-1.62
Solubility	8.50e+00 mg/ml ; 2.40e-02 mol/l
Class	Very soluble
Log S (Ali)	-2.58
Solubility	9.42e-01 mg/ml ; 2.66e-03 mol/l
Class	Soluble
Log S (SILICOS-IT)	0.40
Solubility	8.94e+02 mg/ml ; 2.52e+00 mol/l
Class	Soluble
PHARMACOKINETICS	
GI absorption	Low
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No

CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K p (skin permeation)	-8.76 cm/s
DRUGLIKENESS	
Lipinski	Yes; 1 violation: NHorOH>5
Ghose	No; 1 violation: WLOGP<-0.4
Veber	No; 1 violation: TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 2 violations: TPSA>150, H-don>5
Bioavailability Score	0.11
MEDICINAL CHEMISTRY	
PAINS	1 alert: catechol_A
Brenk	2 alerts: catechol, michael_acceptor_1
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	4.16

QUERCETIN



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

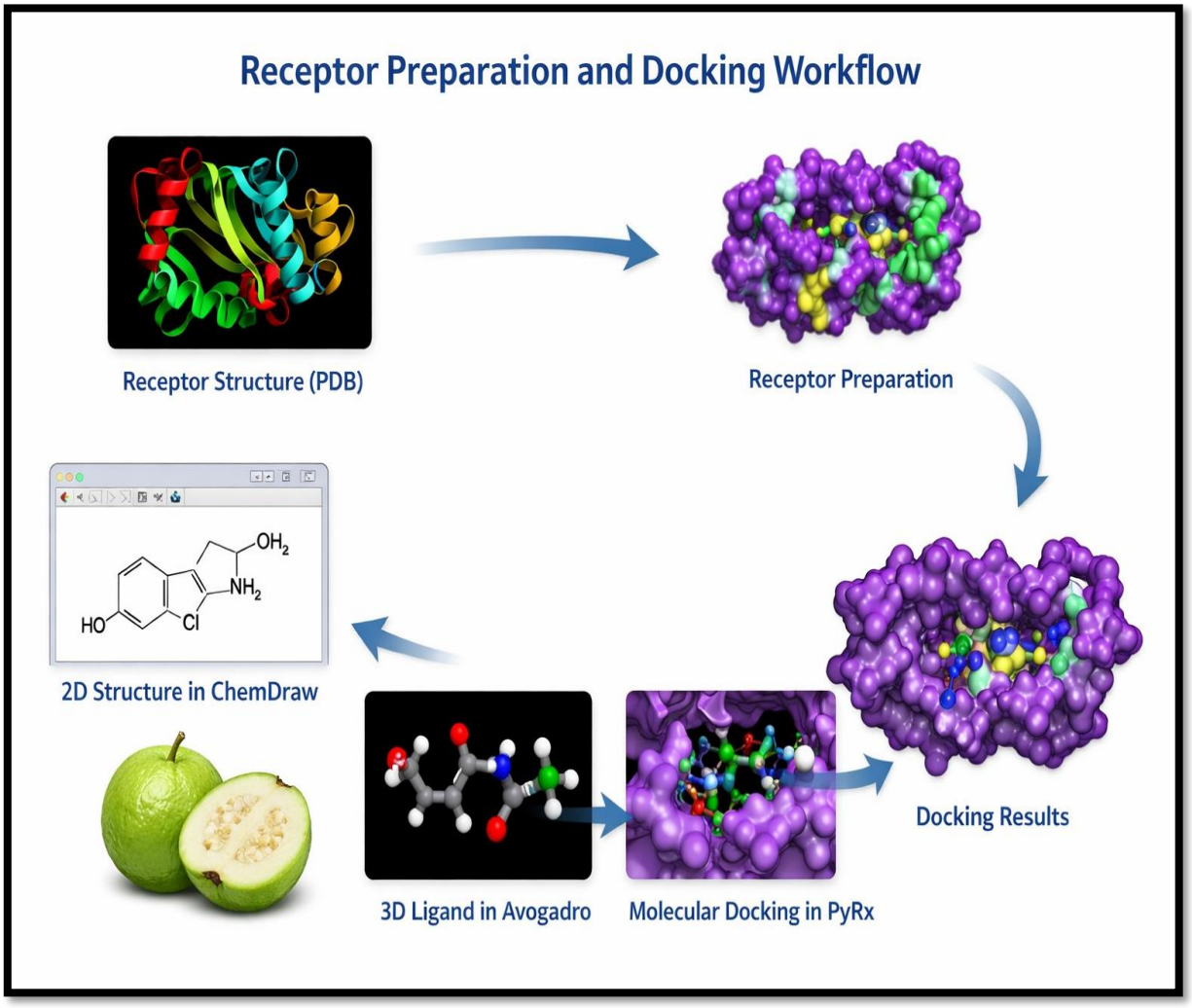
LIPOPHILICITY

Log P o/w (iLOGP)	1.63
Log P o/w (XLOGP3)	1.54
Log P o/w (WLOGP)	1.99
Log P o/w (MLOGP)	-0.56
Log P o/w (SILICOS-IT)	1.54
Consensus Log P o/w	1.23

WATER SOLUBILITY	
Log S (ESOL)	-3.16
Solubility	2.11e-01 mg/ml ; 6.98e-04 mol/l
Class	Soluble
Log S (Ali)	-3.91
Solubility	3.74e-02 mg/ml ; 1.24e-04 mol/l
Class	Soluble
Log S (SILICOS-IT)	-3.24
Solubility	1.73e-01 mg/ml ; 5.73e-04 mol/l
Class	Soluble
PHARMACOKINETICS	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K p (skin permeation)	-7.05 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

Steps In Molecular Docking :



Tools and techniques of structure drawing

PubChem

PubChem Structure Search allows the PubChem Compound Database to be to be queried. by chemical structure or chemical structure pattern. The PubChem Sketcher allows a query to be drawn manually. Users may also specify the structural query input by PubChem Compound Identifier (CID) , SMILES , SMARTS , InChI , Molecular Formula , or by upload of a supported structure file format .(10)

Chemdraw

Chem Draw includes Struct=Name, Chem Draw/Excel and Chem NMR. Create stereo chemically correct structures from chemical names, and get accurate IUPAC names for structures. Estimate NMR spectra from a Chem Draw structure with direct atom to spectral correlation. The Chem Draw ActiveX/Plugin adds chemical intelligence to your browser for querying databases and displaying information.

UC has a site licence for Cambridge Soft Chem Draw Prime and PerkinElmer Chem Draw Professional for use on UC computers. Log a Ticket to ITS for it to be pushed to the Software Centre on a particular computer.

Drawing 2d structure:-You can search the PDB archive for a specific ligand or similar ligands based on the 2D chemical drawing of a molecule. In doing so you can use the graphical interface to draw a molecule of interest or load either the SMILES or InChI descriptors. Both chemical descriptors (SMILES and InChI) of the molecule drawn will be automatically generated and will be available to use as a query. You can also edit a molecule that is drawn or loaded into the tool to add or remove atoms or groups of atoms and then use the new molecule to query the PDB archive. (1) (10).

Draw the 2D chemical structure

There are several ways to make a 2D chemical drawing of a molecule:

Draw the molecule of interest using the options available in the Marvin JS tool

A built-in menu of chemical groups, chains, and rings, along with several keyboard shortcuts provide quick access to the most common editing features for drawing even large and complex molecules.

This option is useful for novel ligands that are not present in the CCD.

Detailed help documentation for using the Marvin JS graphic editor is available can be

found here :

Load the molecule of interest (or a closely related one) using chemical descriptors (e.g.,

InChI or SMILES) or the Chemical Component ID (e.g., ATP, TTT)

This is useful when you have access to chemical descriptors of similar ligands or their

substructure elements

Introduction to Protein Data Bank Format:-

Protein Data Bank (PDB) format is a standard for files containing atomic coordinates. It

is used for structures in the Protein Data Bank and is read and written by many

programs. While this short description will suffice for many users, those in need of

further details should consult the definitive description. The complete PDB file specification provides for a wealth of information, including authors, literature references, and the method of structure determination.

PDB format consists of lines of information in a text file. Each line of information in thefile is called a record. A PDB file generally contains several different types of records,arranged in a specific order to describe a structure.

Preparation of receptor in pdb:

The calculations can be summarized in the following four steps:

(1) preparation of files using AutoDockTools coordinates,

(2) pre-calculation of atomic affinities by using AutoGrid,

(3) docking of ligands by using AutoDock, and (4) analysis of the results applying AutoDockTools.

Generating 3D structures in Avogadro:

1) Draw your desired compound in ChemDraw using as much perspective and stereochemical indicators as possible (draw in ring fusion hydrogens explicitly).

2) Save as a .mol file.

3) Open that .mol file in Avogadro and confirm that you want it to attempt to develop a 3Dmodel.

4) Select the energy minimization tool then click start and wait until the structure becomes mostly static then click stop.

5) Select the rotate tool and look for any atoms that look distorted as this is usually an indication that the program selected the wrong stereochemistry for that atom.

6) Select the select atom tool and select the atom in question. Invert the stereochemistry at that position by going to Build -> Invert Chirality in the menu.

7) Repeat 4-6 until the structure is correct.

8) Hit CTRL's to save.

9) Upload the .mol file to the MaxBridge website and click submit job. (8)

Molecular Docking Tool

Molecular Docking to be done with help of PyRX software model. (9)

Interpretation

8hm0

Nature Of Bond	**Compound**			
	Chlorgenic Acid	**Kampferol**	**Myrecetin**	**Quercetin**
Binding energy	-6.7	-7.1	-9.5	-7.8
Conv. H bond	3	2	2	2
C-H bond				
Pi sigma	1	2		1
Pi cation				
Unfav. Donor-Donor				
Pi alkyl		2	1	9
Pi Pi stacked				1
Pi anion				
Pi Pi T shaped			1	
Interacting amino acid	ARG A:823, ARG A:974 GLU A:830	ASP A:654, GLU A:471	GLU A: 10, ASN A:322	MET C:218, THR C:271

In docking studies, the compound exhibited highest binding affinity towards 8hm0 -

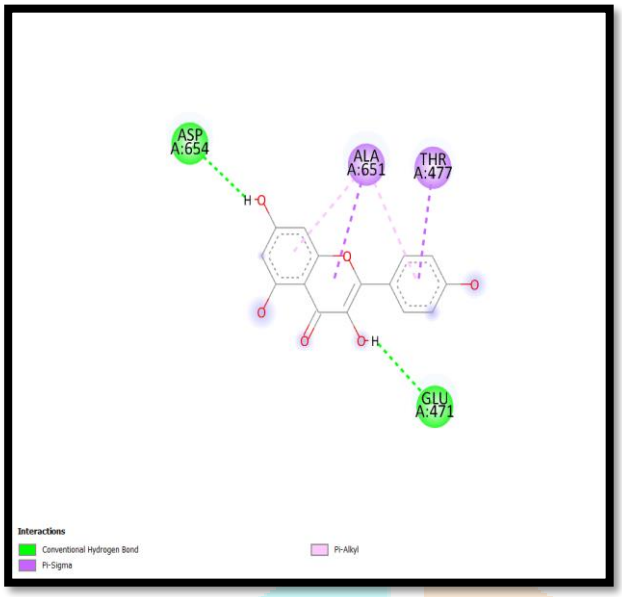
1) The demonstrated highest binding affinity of **Myrecetin -9.5kcal/Mol** towards **8hm0** receptor and formed **2 hydrogen bonds** with amino acid residues *GLU A: 10, ASN A:322* and formed other bonds by interacting with ,other amino acid residues *THR A:326, HIS A:12, MET A:492*.

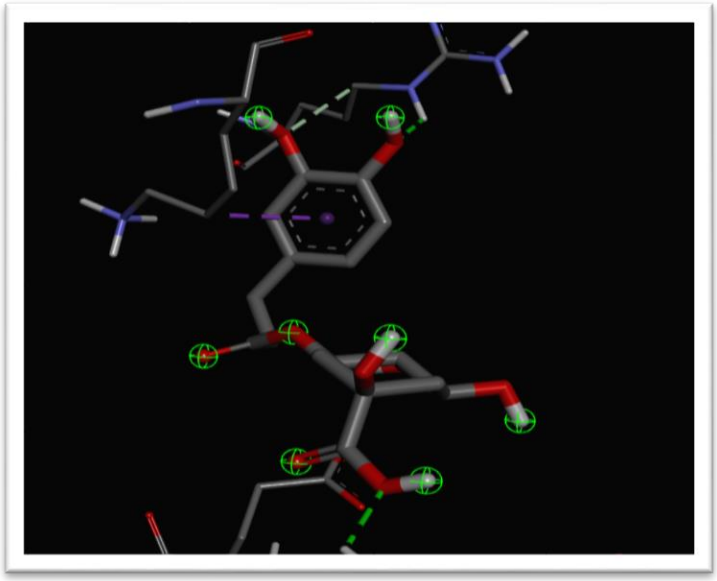
2) The **Quercetin** compound showed good binding affinity of **-7.8 kcal/mol** and form **2 hydrogen bonds** with amino acids *MET C:218, THR C:271* and formed other bonds with Amino acid residues *SER C:272, MET C:218, ILE C:245, ILE C:220, VAL C:264, VAL C:266, LYS C:243 LYS C: 268, PHE C:272.*

3) The **Kampferol** compound showed moderate binding affinity of **-7.1 kcal/mol** and form **2 hydrogen bonds** with amino acids *ASP A:654, GLU A:4*71, and form other bonds with amino acid residues *ALA A:651, THR A: 477, ALA A:651*.

4) The **Chlorogenic acid** compound showed Moderate binding affinity of **-6.7 kcal/mol** and form **3 hydrogen bonds** with amino acids *ARG A:823, ARG A:974 GLU A:830*, and formed other bonds with amino acid residues *LYS A:847, ARG A:823.*

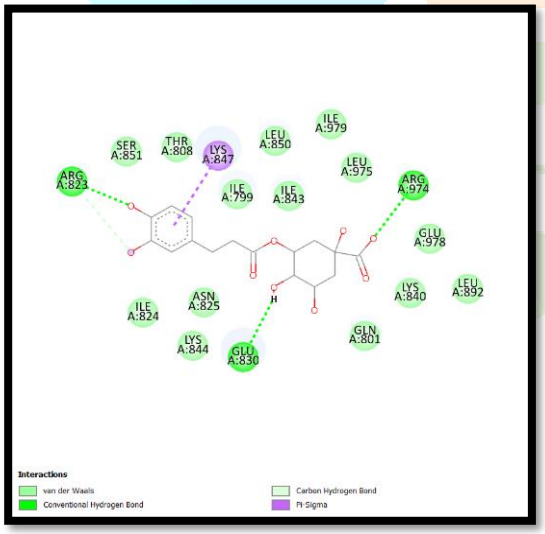
Chlorogenic Acid

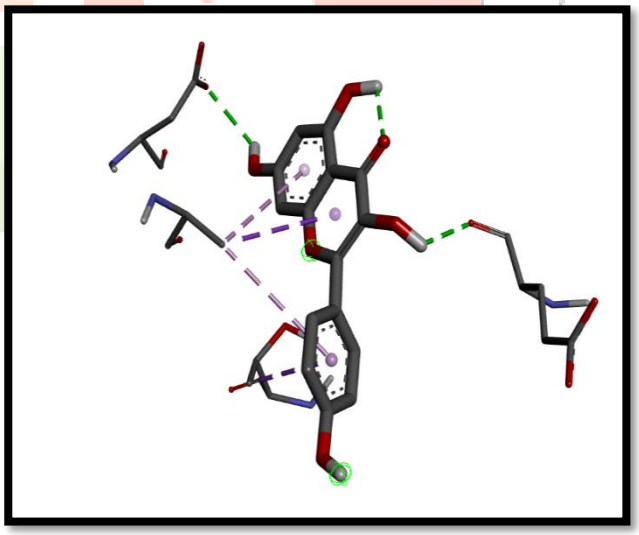




2D Structure **3D Structure**

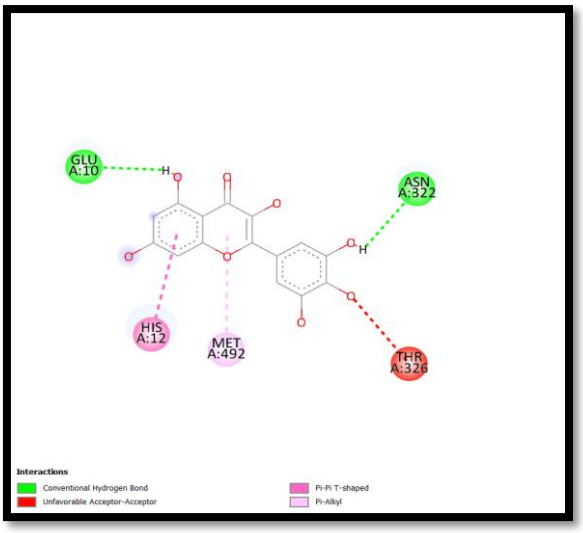
Kampferol

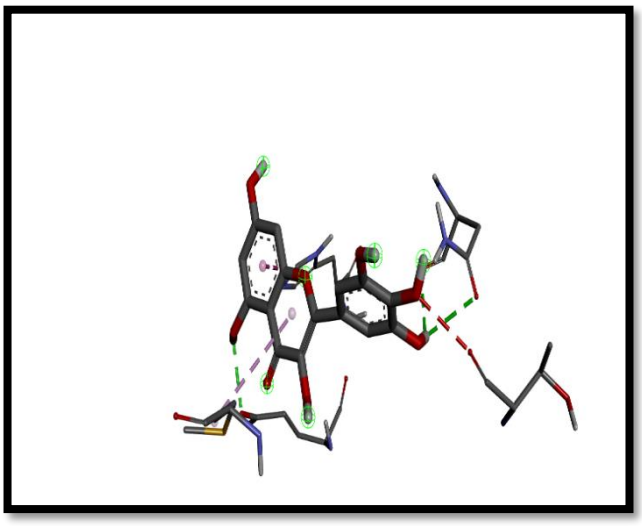




3D Structure

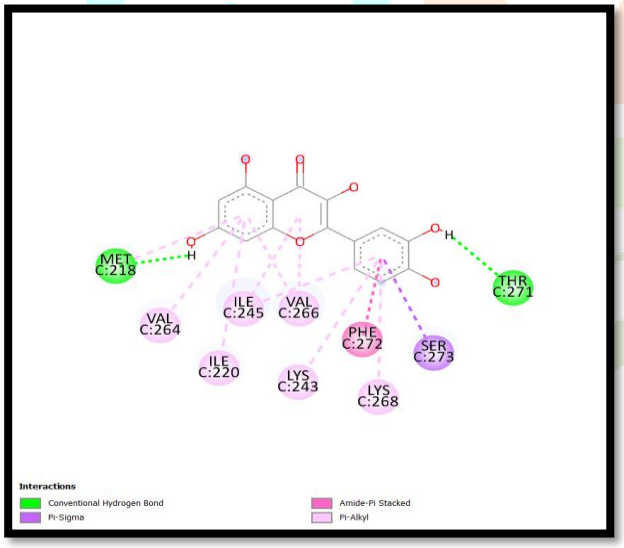
Myrecetin

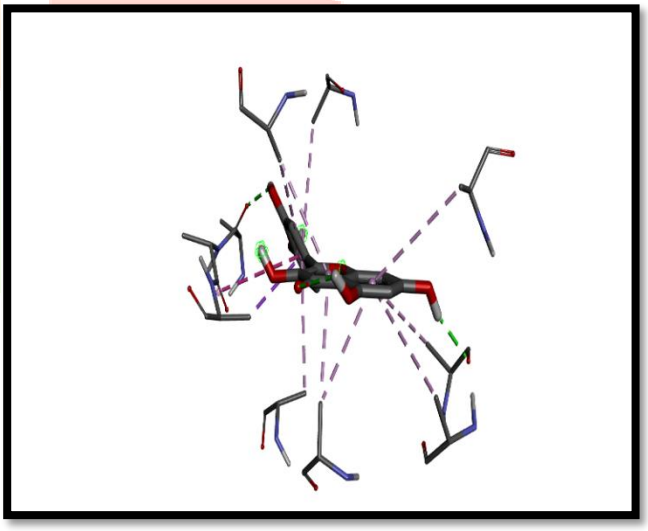




2D Structure **3D Structure**

Quercetin





2D Structure **3D Structure**

2v54

Nature Of Bond	**Compound**			
	Chlorogenic Acid	**Kampferol**	**Myrecetin**	**Quercetin**
Binding energy	-9.1	-7.6	-7.3	-7.3
Conv. H bond	7	2	8	7
C-H bond	1			
Pi sigma	1			
Pi cation		3		
Unfav. Donor-Donor				
Pi alkyl		1	2	2
Pi Pi stacked	1			
Pi anion		3		
Pi Pi T shaped		1		
Interacting amino acid	ARG B:41, ASP B:13, GLU B:142, ARG B:41LYS B:17, PHE B:68, ARG B:72	ARG A:93, LYS A:14	GLU B:142, GLU B:145, LYS B:17, THR B:18, GLY B:16	GLU B:142, LYS B:4, LYS B:17, THR B:8

In docking studies, the compound exhibited highest binding affinity towards 2v54 -

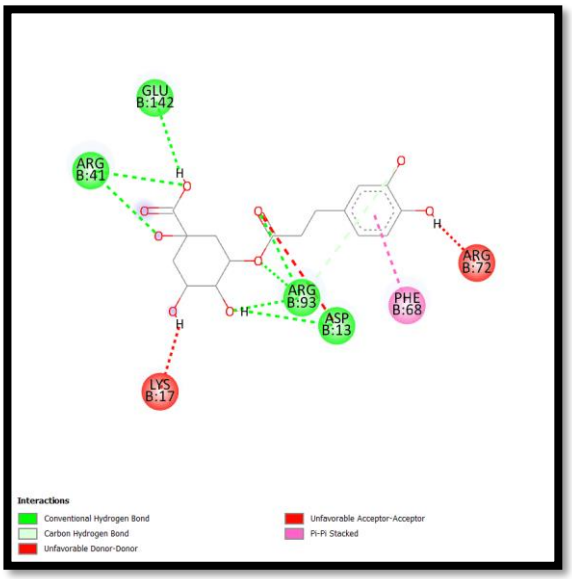
1) The **Chlorogenic acid** demonstrated highest binding affinity of -l**9.1Kcal/mol** towards 2v54 receptor and formed **7 hydrogen bonds** with amino acid residues *ARG B:41, ASP B:13, GLU B:142, ARG B:41*, and formed other bonds by interacting with other amino acid residues *LYS B:17, PHE B:68, ARG B:72.*

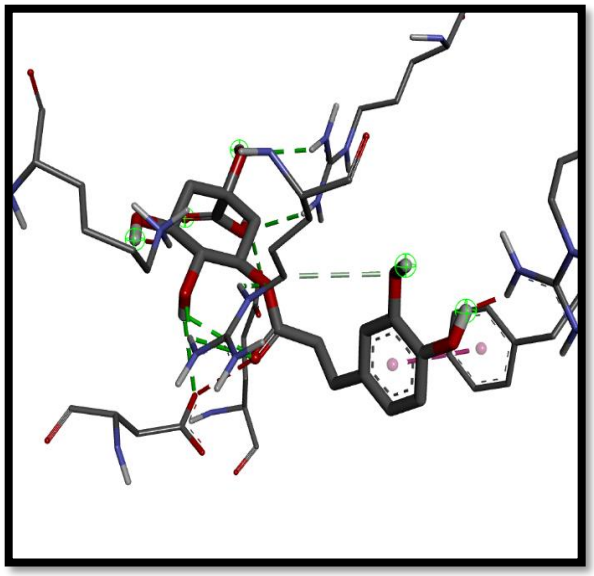
2) The **kampferol** compound showed good binding affinity of **-7.6 kcal/mol** and form 2 hydrogen bonds with amino acids *ARG A:93, LYS A:14*, and formed other bonds with Amino acid residues *LYS A:17, SER A:15, ASP A:13, LEV A:53, TYR A:101.*

3) The **Myrcetin** compond showed moderate binding affinity of **-7.3kcal/mol** and form **8 hydrogen bonds** with amino acids *GLU B:142, GLU B:145, LYS B:17, THR B:18, GLY B:16,* and form other bonds with amino acid residues *THRB:19, ARG B:137, LYS B:14.*

4) The **Quercetin** compound showed Moderate binding affinity of **-7.03kcal/mol** and form **7 hydrogen bonds** with amino acids *GLUB:142, LYS B:4, LYS B:17, THR B:8*, and formed other bonds with amino acid residues *GLU B:145, LYS B:14.*

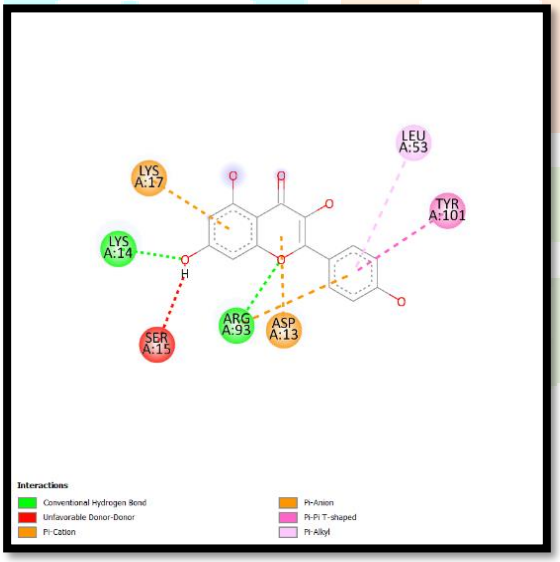
Chlorogenic Acid

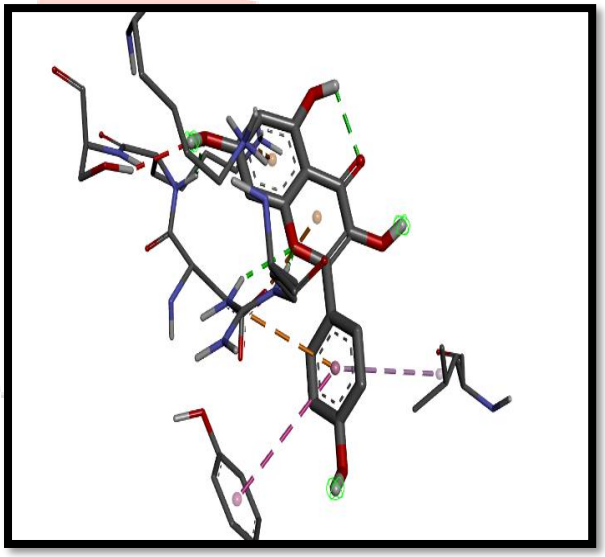




2D Structure **3D Structure**

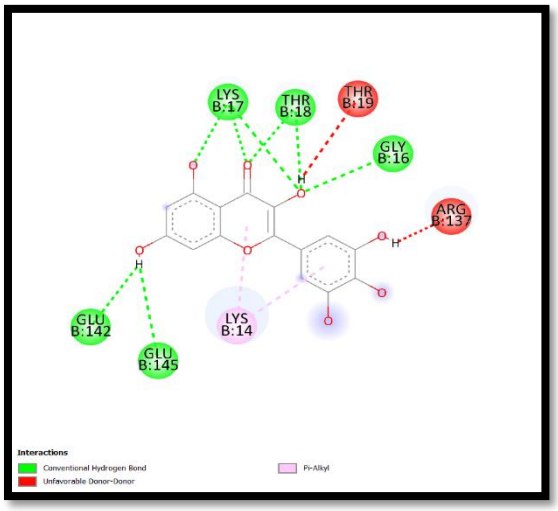
Kampferol

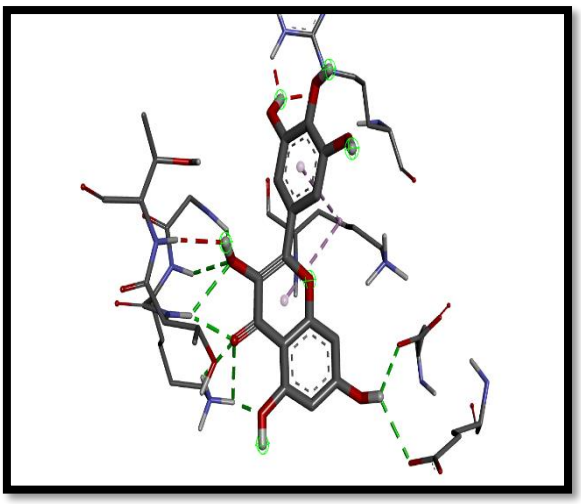




2D Structure **3D Structure**

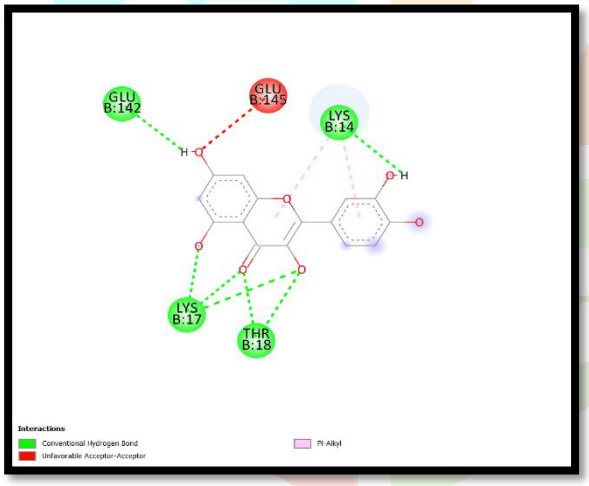
Myrecetin

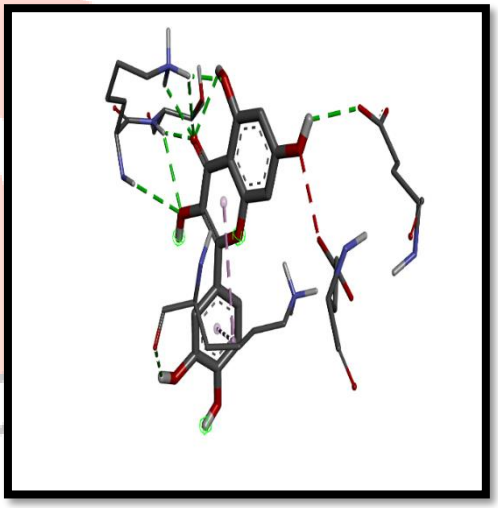




2D Structure **3D Structure**

Quercetin





2D Structure **3D Structure**

Result

Based on the study conducted on the drug likeness properties of phytoconstituents from Psidium guajava (guava) and their molecular docking on monkeypox virus, it was found that the phytoconstituents exhibited antiviral activity against the monkeypox virus. This suggests that the compounds present in Psidium guajava have the potential to inhibit the replication or infectivity of the monkeypox virus. It's important to note that while these findings indicate promising antiviral activity, further research and testing are typically required to validate these results and determine the potential of Psidium guajava phytoconstituents as a treatment or preventive measure for monkeypox virus.

Conclusion

The research involved the identification and extraction of various phytoconstituents from Psidium guajava using appropriate laboratory technique. Psidium guajava exhibited favorable drug-like properties, such as optimal molecular weight, logP values, and compliance with Lipinski's rule of five. These findings suggested that these compounds have the potential to be developed into drug candidates for the treatment of Monkeypox virus infections.

The molecular docking simulations provided insights into the binding interactions between the

identified phytoconstituents and the Monkeypox virus target proteins. The docking results revealed specific binding sites and potential mechanisms of action, highlighting the ability of these compounds to interfere with the viral replication and infectivity processes.

Expected Outcomes:

- The project on drug likeness properties of Psidium guajava and their molecular docking against monkeypox virus could have several expected outcomes. Here are some potential outcomes:
- Identification of bioactive compounds: The project may involve screening Psidium guajava extracts or its isolated compounds for potential bioactive molecules. The outcome could be the identification of specific compounds with drug-like properties, such as antiviral activity against monkeypox virus.
- Evaluation of drug likeness properties: The project may involve assessing the drug likeness properties of the identified compounds. This evaluation could include analyzing properties like molecular weight, lipophilicity, solubility, and other physicochemical characteristics that are important for drug development.
- Molecular docking studies: Molecular docking involves the computational prediction of the binding interactions between the identified compounds and specific target proteins or enzymes of the monkeypox virus. The outcome of these docking studies could be the identification of potential compounds that have a strong binding affinity for the target proteins, suggesting their potential as antiviral agents.
- Prediction of pharmacokinetic properties: The project may also involve predicting the pharmacokinetic properties of the identified compounds. This could include estimating parameters such as absorption, distribution, metabolism, and excretion (ADME) tassess the compounds' potential bioavailability and suitability as drug candidates.
- In vitro or in vivo studies: Depending on the scope of the project, there could be further experimentation involving in vitro or in vivo studies to validate the efficacy of the identified compounds. These studies could include testing the compounds for antiviral activity in cell culture models or assessing their therapeutic effects in animal models of monkeypox infection.
- Contribution to drug discovery: The ultimate goal of the project would be to contribute to the development of potential therapeutic agents against monkeypox virus. If the project successfully identifies compounds with strong antiviral activity, it could lay the foundation for further research and development of drugs that can combat monkeypox infections effectively.
- It's important to note that these outcomes are hypothetical and the actual results would depend on the specific methodologies, resources, and findings of project.

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6.https://journal.umpr.ac.id/index.php/jmd.
7.http://www.swissadme.ch/.
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9.https://pyrx.sourceforge.io/.
10.https://pubchem.ncbi.nlm.nih.gov/compound/Kaempferol, Querecetin, myrecetin, chlorogenic acid/.