In-silico study of Hesperidin, Epigallocatechin (EGCG), Kaempferol and Quercetin

Soham Chatterjee (Soham180808@gmail.com)
Cp Goenka School
Smarajit Maiti
Oriental Institute of Science and Technology, Midnapore, 721102, India
Amrita Banerjee
Oriental Institute of Science and Technology, Midnapore, 721102, India
Mehak Kanwar
Oriental Institute of Science and Technology, Midnapore, 721102, India

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Soham Chatterjee and Professor. Smarajit Maiti

1) Student 7th Grade, Academic Department, Bhaktivedanta Swami Mission School, Shastri Nagar, Andheri West, Mumbai -400053

2) Professor , Academic Department, ,Department of Biochemistry and Biotechnology, Cell and Molecular Therapeutics Laboratory

Oriental Institute of Science and Technology, Midnapore, India

3)Amrita Bannerjee-Assistant Professor

4)Mehak Kanwar-

Correspondence : Soham Chatterjee

No. – 9167205807

Email –Aditichatterjee77@gmail.com

Professor . Smarajit Maiti

No.- 7001836865

Email - maitism@rediffmail.com

3)Amrita Bannerjee

Email-bamrita.bioinfo@gmail.com

4)Mehak Kanwar-

kanwarmuskan8@gmail.com

Conflicts of interest – None

Special Note- A part of this research has been conducted by Soham Chatterjee, One of the youngest researchers across the world and his age is only 12.

Abstract-

SARS-Cov-2 or COVID-19 has caused a global disaster and catastrophe which has consequently led to a pandemic for the last two decades, the world has faced coronaviruses similar to SARS-Cov-2 such as SARS-Cov and Mers-Cov .

In this study, a wide range of proteins such as Plpro(Papain like Protease) ,Rdrp(RNA-Dependent-

RNA-Polymerase),Mpro or 3cl Protease and Spike Protein. The selected proteins were listed retrieved from RCSB PDB(https://www.rcsb.org/)

And Zhang lab (https://www.zhanglab.ccmb.med.umich.edu/COVID-19/) with their corresponding and respective

PDB-ID .The 3d Structures or 2D Structures of these molecules were selected on the sole basis of resolved resolution (in Å)of the structures during the X-ray crystallography and Electron Microscopy. Structures were retrieved in .pdb format .

The three dimensional ligand molecules were retrieved from PubChem chemical structure

In Spatial Data Base (.SDF)format .The respective ligand molecules are ; Hesperidin,Kaempferol ,Quercetin,Epigallocatechin.

This molecular docking shows significant data of polyphenols,flavonoids and bioflavonoids inhibiting SARS-Cov-2 proteins which could lead to conclusive data for treatment of polyphenols,flavonoids and bioflavonoids against SARS-Cov-2.

Introduction –

1)Hesperidin is a flavonoid (1),in immense quantities of citrus species (2),has numerous anti-oxidant properties(3) and anti-inflammatory properties (3),(4),also is a significant flavonoid against obesity (5) and has anti-cancer properties (6) and is also is a neuroprotective flavonoid (7).

Hesperidin has anti-diabetic (8) properties by regulating and targeting the selective factors of diabetes effective renal function (8) and moderated signaling pathways affecting Diabetes (8).

2)Kaempferol is a flavonoid (9),has immense properties targeting cancer (10) such as breast cancer,(10),(11) and bone cancer (10) and gastric cancer(12).It also inhibits and has therapeutic effects and targets cardiovascular diseases (13),

(14),also has chemo-preventive effective results for cardiovascular diseases (14).Also has multiple anti-inflammatory properties (15).

3)Quercetin reduces blood pressure (16),inhibits and targets and has therapeutic effects on cardiovascular diseases (17),(18) .

Quercetin has several anti-inflammatory properties (20), also inhibits obesity (21),type-2 diabetes (21) and inflammation (20),(21).

4) Epigallocatechin is a polyphenol (22),has therapeutic effects against cardiovascular diseases (23) and metabolic diseases(23), has immense anti cancer properties (24),It also regulates cancer stem cells (24),also interacts with metalloproteinase (24) and has significant regulation and modulation in signalling pathways (24),(25).

In Focus For Sars-Cov-2 :

Molecular Docking of Hesperidin with Plpro(Papain like Protease):

Materials and Methods:

Protein Structure Retrieval-

Plpro(Papain like Protease) which is a component part of the non structural protein (nsp3),(26) .

SARS-Cov-2 Plpro Protease shares high amino acid sequencing with SARS-Cov .(27)

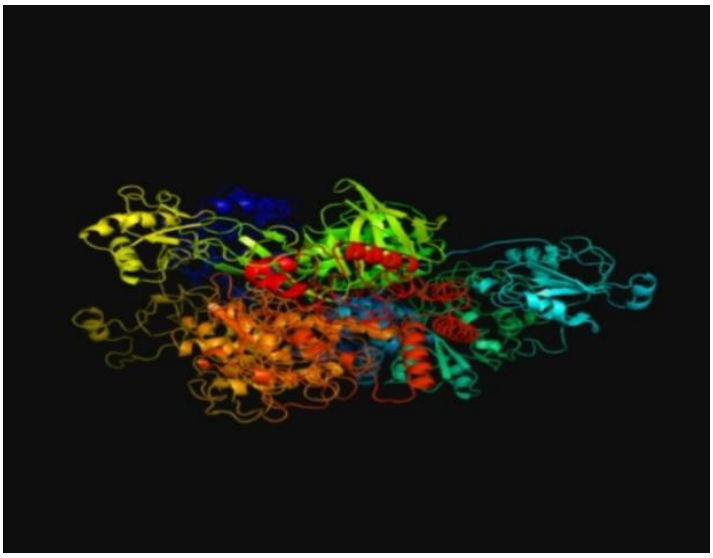
It is essential for viral replication (27)

It is significant for viral polyprotein cleavage and deconjugation of ISGI5 (28).

The electronic microscopic Structure of the Plpro (Papain like Protease) of SARS-Cov-2 was retrieved

From zhanglab- (https://www.zhanglab.ccmb.med.umich.edu/COVID-19/)

N-Terminus _protenase _QHD43415_3



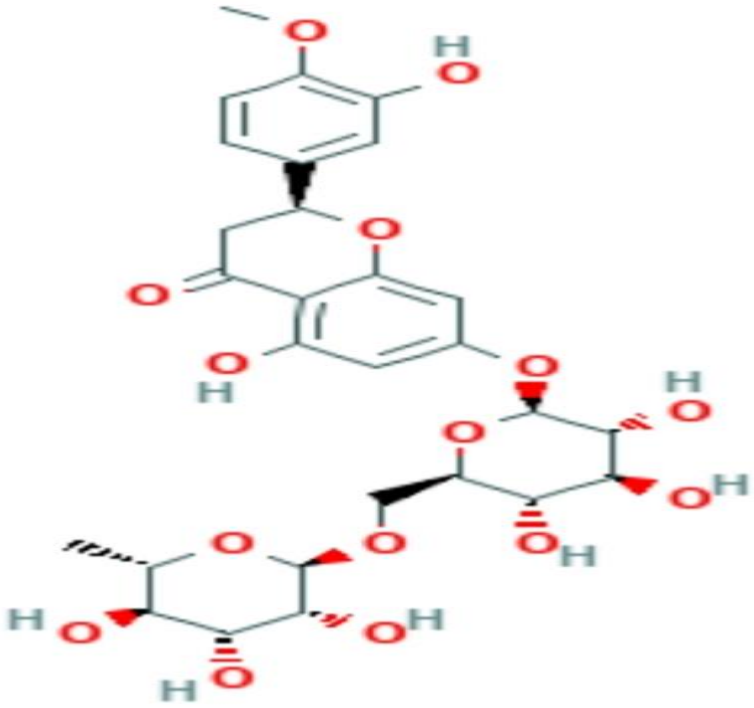
Ligand Structure Retrieval-

The two dimensional Structures molecular structures of Hesperidin were retrieved from the world's largest chemical database which is Pubchem (https://pubchem.ncbi.nlm.nih.gov/).

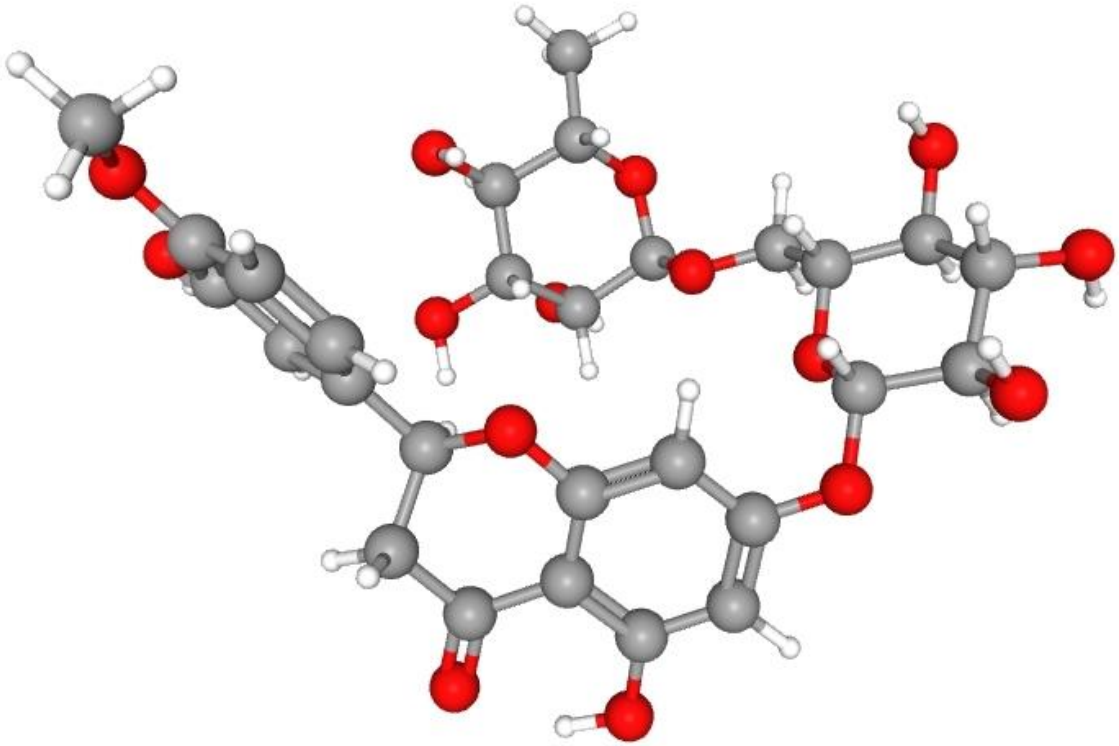
Pubchem ID- 10621

Chemical Formula –-C28H34O15

Two Dimensional Structure Of Hesperidin-



Three Dimensional Structure of Ligand Molecule(Hesperidin)-



Results-

The Ligand Structure-Hesperidin with viral Protein Structure-

N-Terminus _protenase _QHD43415_3 interaction is divided into two tables –

Table C				
Conformation	Binding Energy	Ligand Efficiency	Ki	Intermol energy
1	-8.07	-0.22	1.21	-10.76
2	-5.33	-0.14	122.87	-8.02
3	-6.19	-0.17	28.92	-8.88
4	-5.61	-0.15	77.51	-8.29
5	-5.35	-0.14	119.02	-8.04
6	-6.48	-0.18	17.77	-9.17
7	-5.53	-0.15	88.08	-8.22
8	-5.76	-0.16	60.35	-8.44
9	-6.1	-0.16	33.61	-8.79
10	-6.76	-0.18	11.15	-9.44

Binding Energy,Ligand Efficiency, Ki value and Intermol Energy

N-terminus_protenase_QHD43415_3							
vdw hb desolv energy	electrostatic energy	total internal	torsional energy	unbound energy	ref RMS	cIRMS	Hydrogen Bond energy
-7.52	-3.24	-1.78	2.68	-1.78	110.11	0	-0.239
-6.63	-1.39	-3.24	2.68	-3.24	130.94	0	-0.137
-6.12	-2.76	-2.84	2.68	-2.84	109.37	0	nb
-6.31	-1.98	-2.82	2.68	-2.82	129.64	0	nb
-7.46	-0.58	-3.52	2.68	-3.52	82.22	0	nb
-6.46	-2.71	-3.16	2.68	-3.16	116.41	0	nb
-5.63	-2.59	-2.15	2.68	-2.15	111.9	0	nb
-7.58	-0.86	-3.01	2.68	-3.01	84.08	0	nb
-6.15	-2.64	-3.08	2.68	-3.08	108.07	0	nb
-6.7	-2.74	-3.09	2.68	-3.09	117.71	0	nb

Vdw hb desolv energy ,electrostatic energy,total internal ,torsional energy ,unbound energy ,ref Rms ,cRMS,Hyrdogen Bond Energy .

Conclusion-

Ligand Efficiency is moderately inhibiting against the Plpro(papain like Protease).

Binding Energy is also moderate, therefore Hesperidin can inhibit Plpro(Papain like Protease) and inhibit viral polyprotein cleavage and viral replication (27),(28).

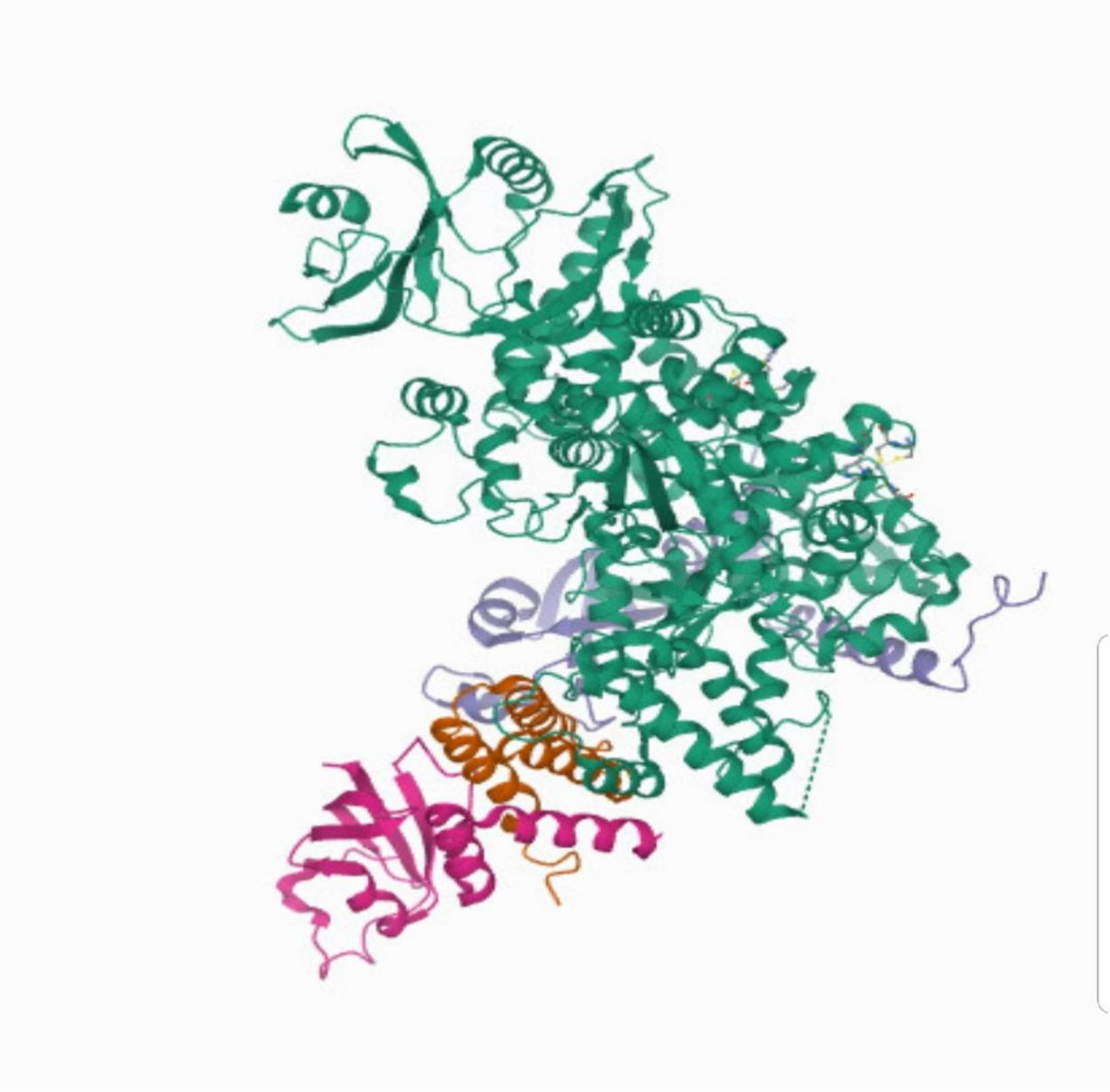
2)Virtual Screening of Kaempferol against RDRP(RNA-DEPENDENT-RNA-POLYMERASE)-

Protein Structure Retrieval-

RDRP (nsp12) is a crucial for viral replication and transcription (29),It is the central part of the viral polymerase family (29),therefore being a crucial drug target .

The electronic microscopic Structure of the RDRP(RNA-DEPENDENT-RNA-POLYMERASE)

Was retrieved from RCSB PDB -7btf -RDRP (https://www.rcsb.org/).



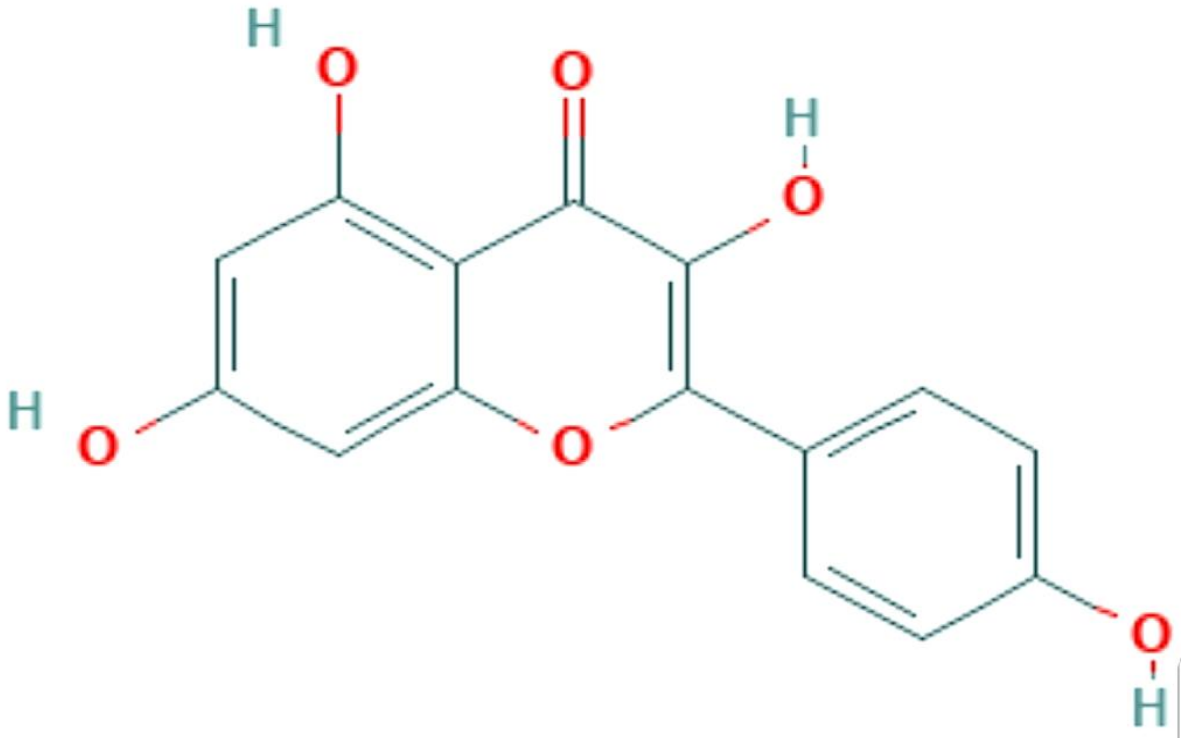
Ligand Structure Retrieval-

The three dimensional structures and two dimensional Structures were retrieved from the worlds largest chemical database :Pubchem.

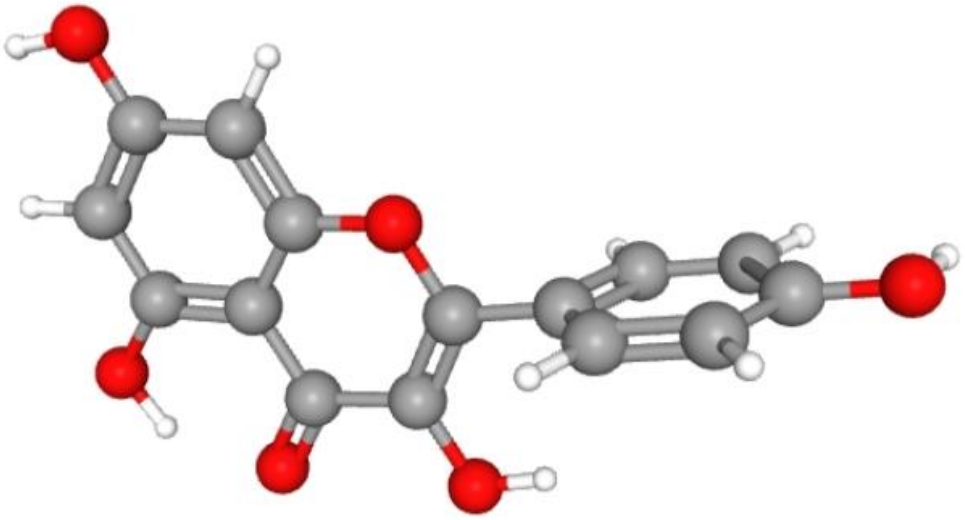
Pubchem ID-5280863 Pubchem Formula- C15H1O6

(https://pubchem.ncbi.nlm.nih.gov/).

Two dimensional Structure –



Three Dimensional Structure-



Results-

The Molecular interaction of Kaempferol with RDRP is divided into two tables -

Table G			
Conformation	Binding Energy	Ligand Efficiency	Ki
1	-3.27	-0.16	4.02
2	-3.64	-0.17	2.15
3	-4.34	-0.21	660.45
4	-4.08	-0.19	1.02
5	-2.92	-0.14	7.19
6	-3.78	-0.18	1.7
7	-4.62	-0.22	408.27
8	-3.65	-0.17	2.11
9	-3.67	-0.17	2.06
10	-3.06	-0.15	5.74

Binding Energy,Ligand efficiency,Ki value

7btf_SARS-CoV-2 RNA-dependent RNA polymerase in complex with cofactors in reduced condition											
Intermol energy	vdw hb desolv energy	electrostatic energy	total internal	torsional energy	unbound energy	ref RMS	cIRMS	hydrogen Bond Energy			
-4.76	-4.66	-0.1	-1.53	1.49	-1.53	221.42	0	-0.741	-2.478		
-5.13	-5.03	-0.11	-1.57	1.49	-1.57	195.61	0	-3.095			
-5.83	-5.58	-0.25	-1.54	1.49	-1.54	191.55	0	-3.402	-0.063		
-5.58	-5.47	-0.1	-1.56	1.49	-1.56	209.14	0	-1.964			
-4.42	-4.29	-0.12	-1.57	1.49	-1.57	228.3	0	-4.367			
-5.27	-5.14	-0.12	-1.46	1.49	-1.46	241.72	0	-3.313			
-6.11	-6.03	0.08	-1.53	1.49	-1.53	233.14	0	-1.651			
-5.14	-4.8	-0.34	-1.57	1.49	-1.57	266.54	0	-4.388	-4.386	-0.535	-4.541
-5.16	-5.07	-0.09	-1.57	1.49	-1.57	202.1	0	-2.047			
-4.55	-4.27	-0.28	-1.57	1.49	-1.57	178.74	0	-6.526			

Intermol energy ,Electrostatic energy ,total internal energy ,torsional energy , unbound energy,ref RMS , cRMS ,Hydrogen Bond energy .

Conclusion –

Binding energy with polyprotein nsp12 (RDRP)

And ligand efficiency is moderate , therefore can inhibit the central transcription of the viral genome and replication (29),also as Rdrp complex is with nsp 7,ns8 (30),polyprotein processing can be inhibited by kaempferol.

Co factors of the non-structural protein (nsp12) are nsp 7-8 polymerase complex are vital in abetting of nucleic acid (31).

Therefore Kaempferol has sufficient binding energies,ligand energies for RDRP(RNA-DEPENDENT-RNA-POLYMERASE).

Molecular Docking Kaempferol with 3cl (Mpro Protease) –

The 3cl Protease is a crucial part for translation of polyprotein processing into viral RNA(32),(33).

It is also in complex with 11a and 11b and is enclosed with the cysteine 145 (32),(33).

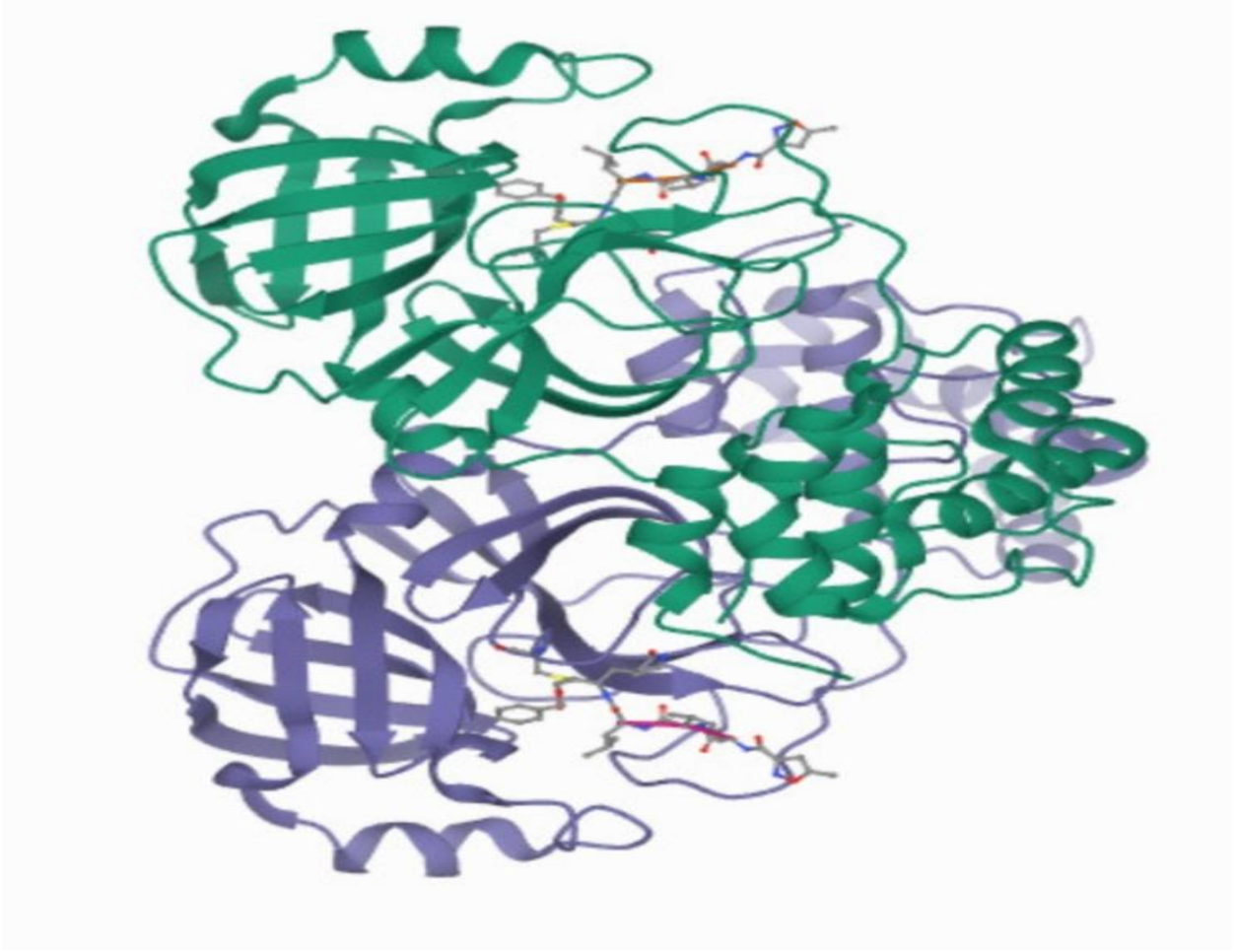
Has significant function of intercession of transcription and processing of polyproteins (32),(33).

Protein Structure Retrieval-

The electronic microscopic and crystal structure of 3cl Protease in complex with N3 inhibitor with Escherichia coli expression system was retrieved from (https://www.rcsb.org/structure/6LU7).

Ligand Structure Retrieval-

The 3d and 2d ligand Structures of Kaempferol were retrieved from the

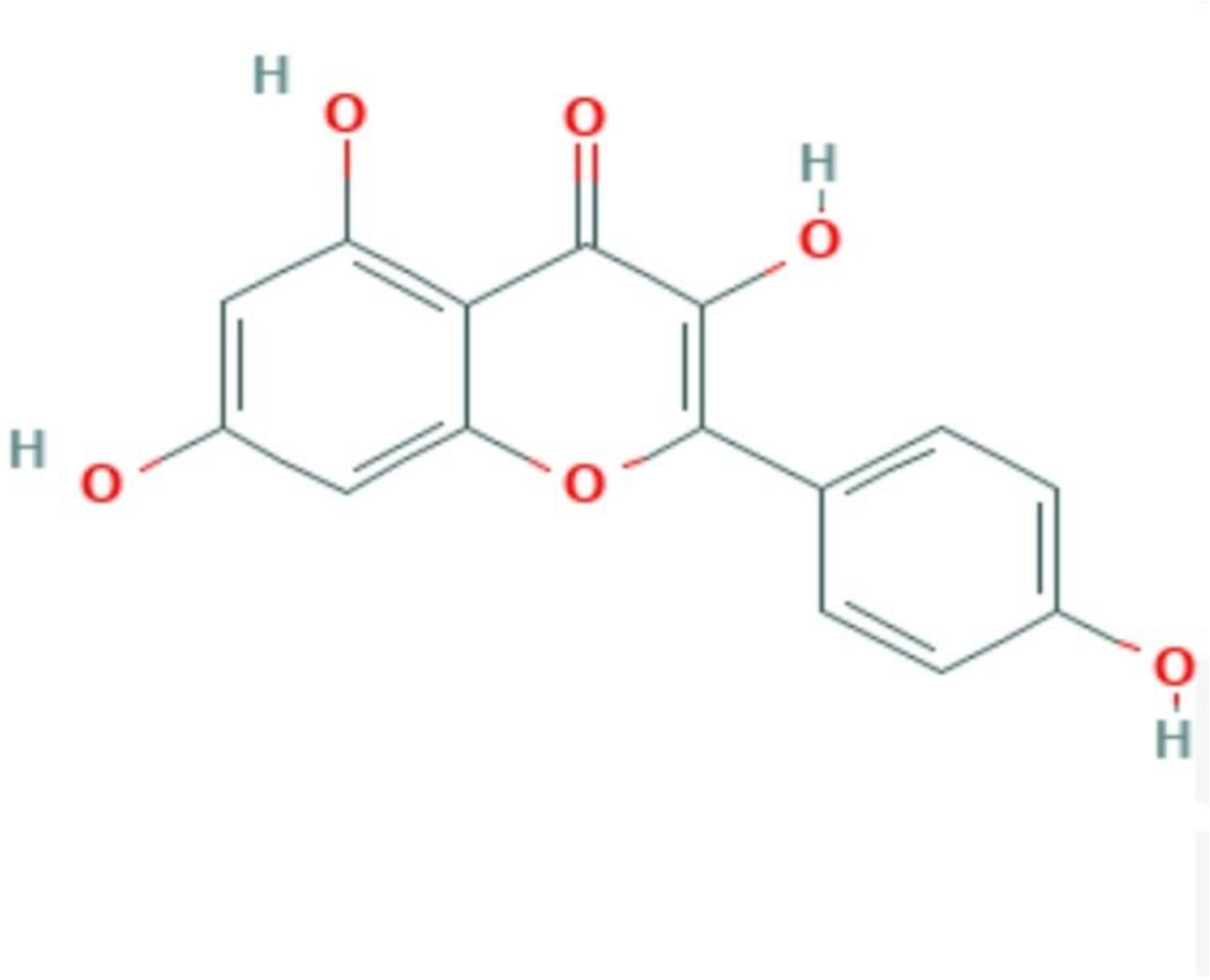


worlds largest database:

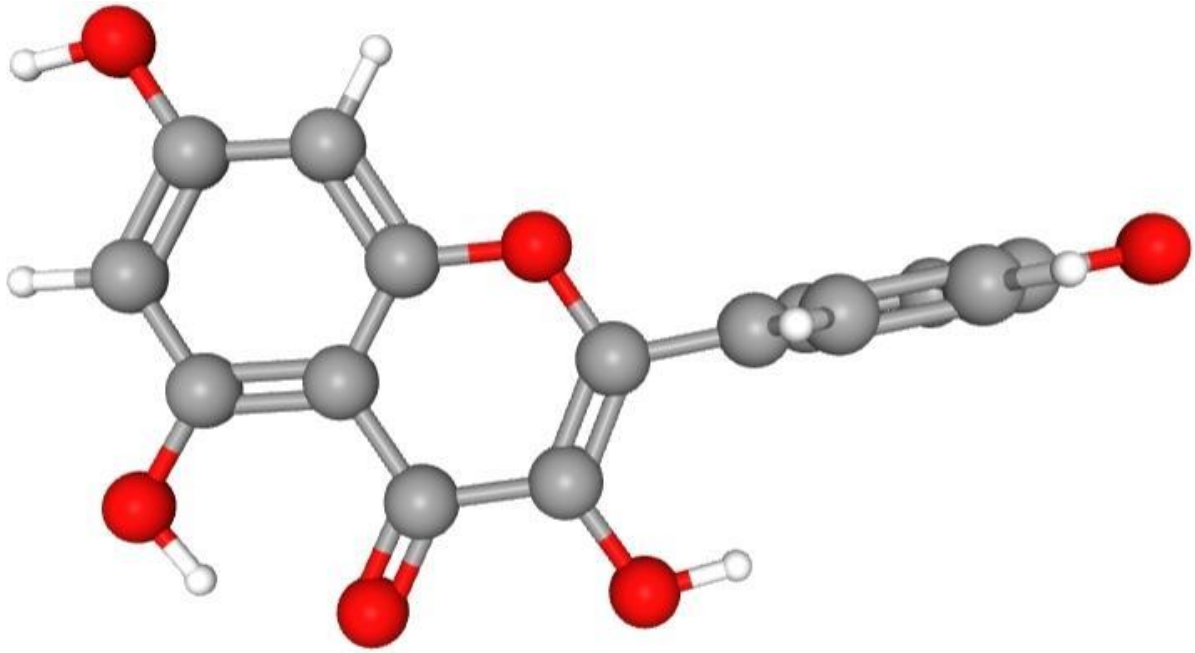
Pubchem .

Pubchem ID -5280863 and Pubchem formula- C15H1O6 . Pubchem link –(https://pubchem.ncbi.nlm.nih.gov/).

Two dimensional Structure-



Three dimensional ligand Structure-



Results-

The molecular interaction of Kaempferol with 3cl Protease is divide into two tables -

Binding Energy,Ligand efficiency,Ki value

Table F			
Conformation	Binding Energy	Ligand Efficiency	Ki
1	-2.59	-0.12	12.63
2	-4.84	-0.23	283.39
3	-3.33	-0.16	3.62
4	-4.88	-0.23	266.88
5	-3.6	-0.17	2.31
6	-4.39	-0.21	605.12
7	-4.09	-0.19	999.76
8	-3.55	-0.17	2.5
9	-3.17	-0.15	4.72
10	-4.36	-0.21	641.86

Intermol energy ,vdw hv desolv energy , electrostatic energy, total

6LU7_The crystal structure of COVID-19 main protease in complex with an inhibitor N3											
Intermol energy	vdw hb desolv energy	electrostatic energy	total internal	torsional energy	unbound energy	ref RMS	clRMS	hydrogen Bond Energy			
-4.08	-4	-0.08	-1.56	1.49	-1.56	64.74	0	nb			
-6.33	-6.05	-0.28	-1.53	1.49	-1.53	62.24	0	-3.97			
-4.82	-4.71	-0.11	-1.48	1.49	-1.48	71.16	0	-2.889			
-6.37	-6.28	-0.09	-1.56	1.49	-1.56	69.78	0	-2.963			
-5.09	-5.03	-0.06	-1.56	1.49	-1.56	78.28	0	-3.807			
-5.88	-5.69	-0.2	-1.57	1.49	-1.57	70.52	0	-5.916	-3.82	-1.522	-2.47
-5.58	-5.33	-0.25	-1.57	1.49	-1.57	59.88	0	-0.097			
-5.04	-4.87	-0.18	-1.51	1.49	-1.51	75.39	0	nb			
-4.66	-4.59	-0.08	-1.55	1.49	-1.55	53.28	0	-4.654			
-5.85	-5.74	-0.11	-1.53	1.49	-1.53	49.65	0	-4.069	-0.623	-5.592	

internal ,torsional energy, Rms ,cRMS,Hydrogen Bond energy .

Conclusion –

Kaempferol has viable small molecular inhibition with the 3cl Protease, with inhibition of translation of the polyprotein processing and cleavage into viral RNA(32,33) .

Molecular Inhibition of the 3cl Protease with the complex 11a and 11b(31),(32) is crucial, Inhibition at small molecular inhibition can inhibit the viral genome complex to replicate ,by inhibiting the transcription of viral polyprotein processing (31),(32).

Molecular Docking of Egcg (Epigallocatechin) with Plpro (Papain like Protease).

Plpro(Papain like Protease) which is a significant part of the non structural protein (nsp3),(26) .

SARS-Cov-2 Plpro Protease has similar high amino acid sequencing with SARS-Cov .(27)

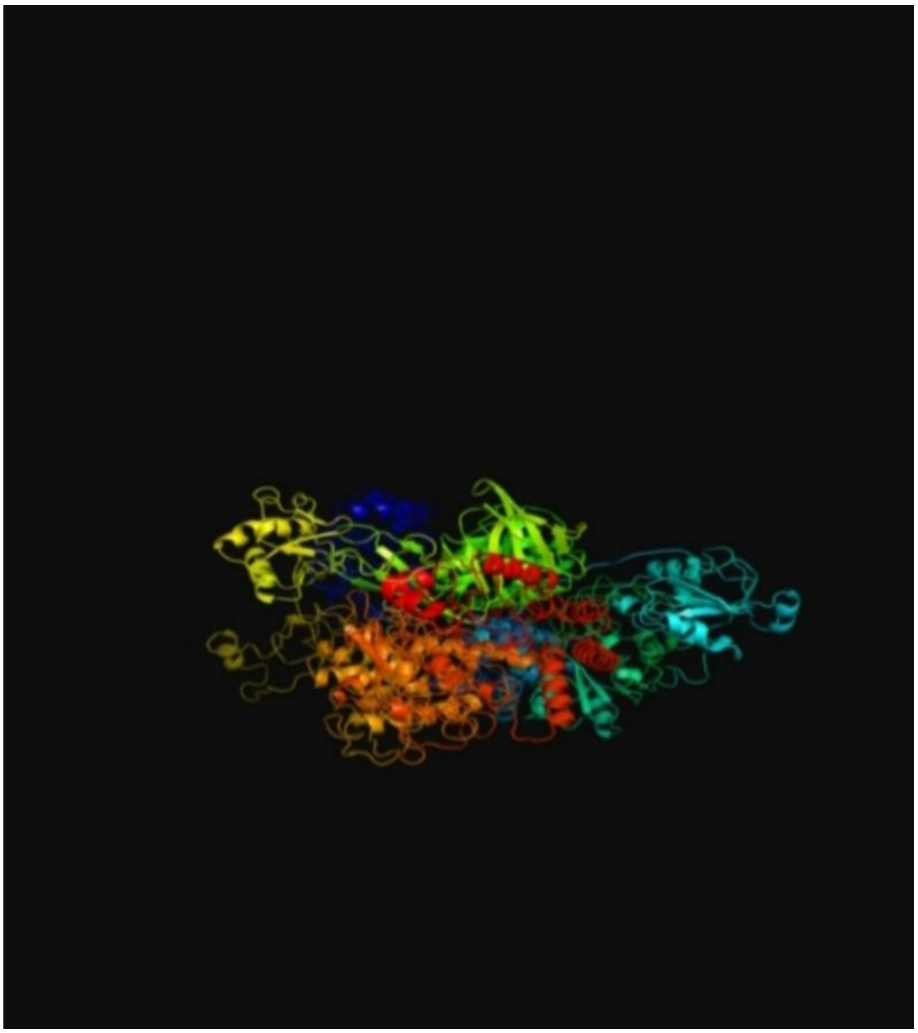
It is essential for viral replication (27)

It is significant for viral polyprotein cleavage and deconjugation of ISGI5 (28).

The electronic microscopic Structure of the Plpro (Papain like Protease) of SARS-Cov-2 was retrieved

From zhanglab- (https://www.zhanglab.ccmb.med.umich.edu/COVID-19/)

N-Terminus _protenase _QHD43415_3



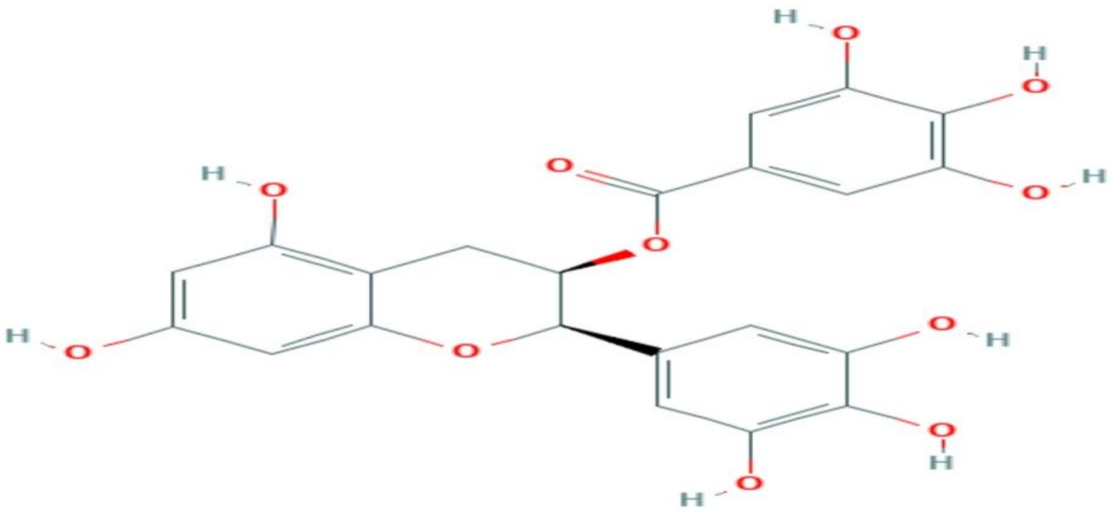
Ligand Structure Retrieval-

The two dimensional structures And three dimensional structures of Epigallocatechin were retrieved from the worlds largest chemical database – Pubchem –(https://pubchem.ncbi.nlm.nih.gov/).

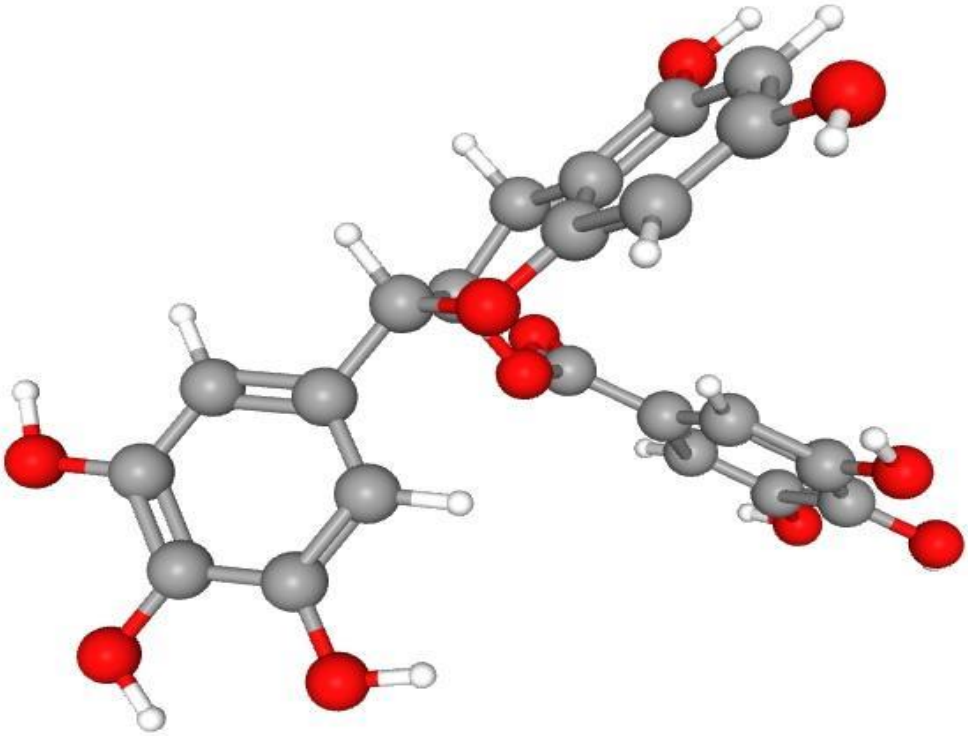
Chemical Formula- C22H18O11

Pubchem ID-65064

Two dimensional Structure of Epigallocatechin-



Three Dimensional Structure of Epigallocatechin-



Results- Interaction Of Epigallocatechin with Plpro divided in 2 tables -

Table C					
Conformation	Binding Energy	Ki	Ligand Efficiency	Intermol energy	vdw hb desolv energy
1	-3.29	3.89	-0.1	-6.87	-6.73
2	-3.17	4.72	-0.1	-6.75	-6.74
3	-2.78	9.21	-0.08	-6.36	-6.02
4	-2.59	12.66	-0.08	-6.17	-6.08
5	-1.9	40.36	-0.06	-5.48	-5.07
6	-1.89	41.37	-0.06	-5.47	-5.33
7	-1.73	53.51	-0.05	-5.31	-5.49
8	-1.46	84.6	-0.04	-5.04	-5.06
9	-1.06	168.34	-0.03	-4.64	-4.54
10	-1.01	183.31	-0.03	-4.58	-4.5

Binding Energy, Ki value, Ligand Efficiency, Intermol energy, vdw hb desolv energy .

N-terminus_protenase_QHD43415_3					
electrostatic energy	total internal	torsional energy	unbound energy	ref RMS	cIRMS
-0.14	-5.22	3.58	-5.22	100.03	0
-0.01	-5.03	3.58	-5.03	100.26	0
-0.34	-5.39	3.58	-5.39	100.41	0
-0.09	-6.22	3.58	-6.22	118.99	0
-0.41	-5.34	3.58	-5.34	123.05	0
-0.14	-5.41	3.58	-5.41	82.51	0
0.18	-6.68	3.58	-6.68	96.71	0
0.01	-5.09	3.58	-5.09	118.5	0
-0.09	-6.64	3.58	-6.64	79.21	0
-0.08	-5.72	3.58	-5.72	117.39	0

Electrostatic energy, total internal energy , torsional energy , unbound energy and ref RMS

cIRMS.

Conclusion –

Epigallocatechin inhibits Plpro(Papain like Protease) at a moderate molecular inhibition which could lead to inhibition of the polyprotein processing (27),(28) and cleavage ,Plpro (nsp3) Protein is a crucial target for molecular inhibition which Epigallocatechin shows at sufficient levels.

Virtual Screening of Quercetin with 3cl Protease-

The 3cl Protease is a extremely significant pfor translation of polyprotein processing into viral RNA(32),(33) .

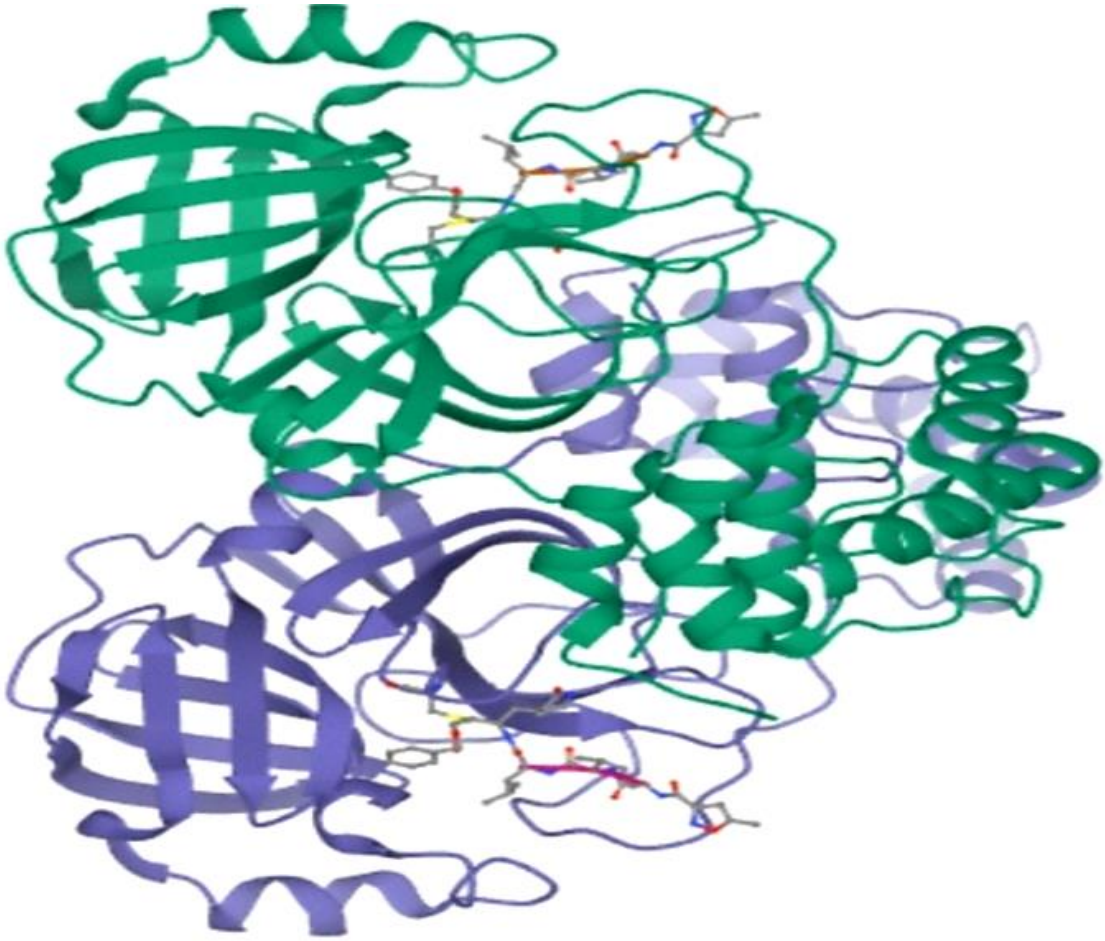
It is also in complex with 11a and 11b and is enclosed with the cysteine 145 (32),(33).

Has significant function of intercession of transcription and processing of polyproteins (32),(33).

Protein Structure Retrieval-

The electronic microscopic and crystal structure of 3cl Protease in complex with N3 inhibitor with Escherichia coli expression system was retrieved from RCSB

(https://www.rcsb.org/structure/6LU7)



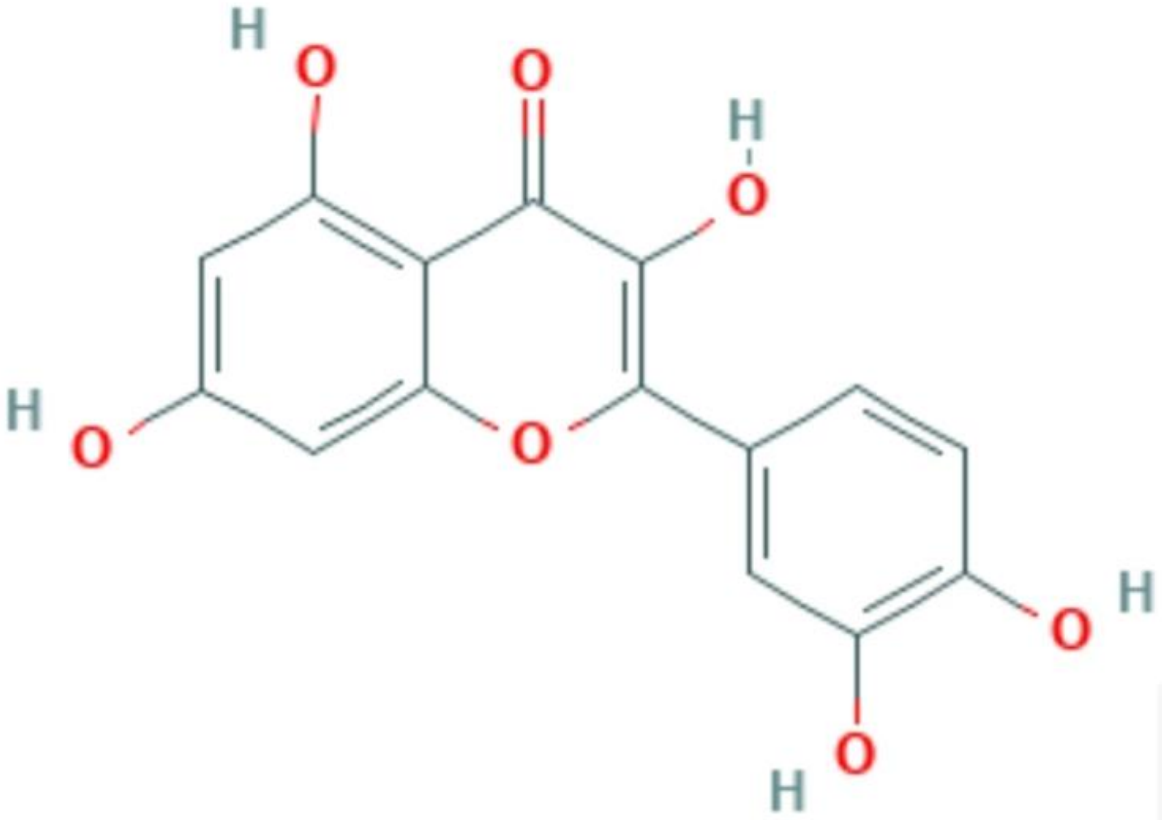
Ligand Structure Retrieval-

The Three Dimensional structures and two dimensional structures of quercetin were retrieved from the worlds largest Chemical database: Pubchem(https://pubchem.ncbi.nlm.nih.gov/). .Chemical Formula of Quercetin-

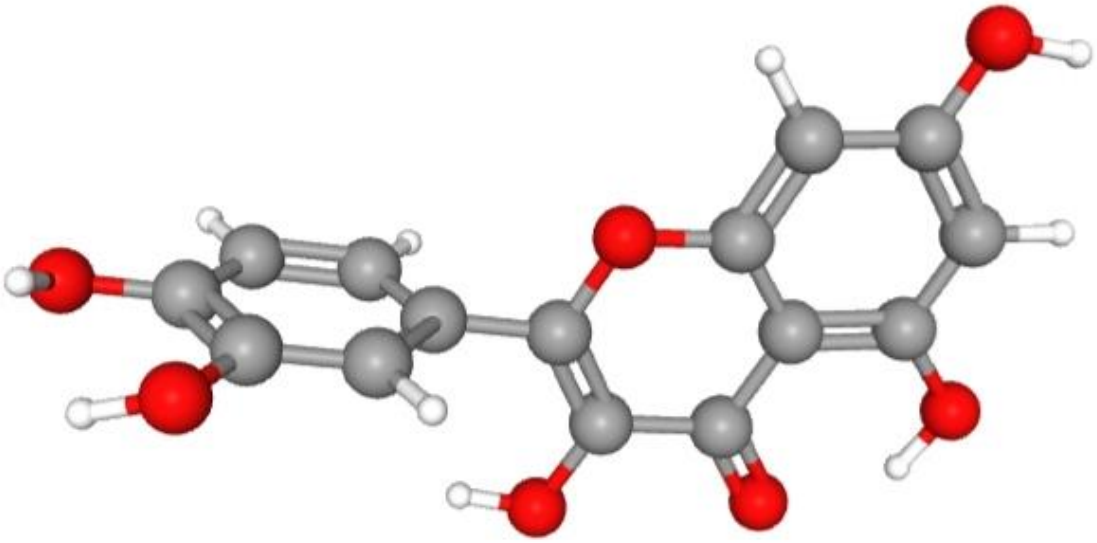
C15H10O7

Pubchem ID :5280343

Two dimensional Structure of Quercetin –



Three Dimensional Structure of Quercetin-



Results-

Molecular Interaction of Quercetin with Mpro or 3cl Protease is divided into two tables -

Table F			
Conformation	Binding Energy	Ligand Efficiency	Ki
1	-3.11	-0.14	5.24
2	-3.59	-0.16	2.32
3	-3.16	-0.14	4.85
4	-3.29	-0.15	3.85
5	-3.11	-0.14	5.25
6	-3.03	-0.14	-5.97
7	-2.78	-0.13	9.19
8	-2.48	-0.11	15.21
9	-3.32	-0.15	3.71
10	-3.02	-0.14	6.11

Binding Energy,Ligand Efficiency and Ki Value

6LU7_The crystal structure of COVID-19 main protease in complex with an inhibitor N3										
Intermol energy	vdw hb desolv energy	electrostatic energy	total internal	torsional energy	unbound energy	ref RMS	cIRMS	hydrogen Bond Energy		
-4.9	-4.44	-0.47	-2.63	1.79	-2.63	77.33	0	-3.652	-2.194	-0.596
-5.38	-5.23	-0.15	-2.21	1.79	-2.21	57.4	0	-0.763	-1.603	
-4.95	-4.81	-0.14	-2.52	1.79	-2.52	60.73	0	nb		
-5.08	-4.82	-0.27	-2.6	1.79	-2.6	74.6	0	-1.432		
-4.9	-4.84	-0.06	-2.64	1.79	-2.64	59.45	0	-1.319		
-4.82	-4.69	-0.13	-2.53	1.79	-2.53	49.57	0	nb		
-4.57	-4.45	-0.12	-2.59	1.79	-2.59	65.05	0	-0.709		
-4.27	-4.22	-0.05	-2.63	1.79	-2.63	80.22	0	-3.93		
-5.11	-4.99	0.12	-2.61	1.79	-2.61	64.88	0	nb		
-4.81	-4.71	-0.1	-2.47	1.79	-2.47	72.91	0	-2.071	-2.988	

Intermol Energy, Vdw hb desolv energy, electrostatic energy ,total internal energy and torsional energy ,unbound energy ,ref RMS,cRMS ,Hydrogen Bond Energy .

Conclusion-

Inhibition of Mpro Protease or 3cl Protease ,Quercetin has molecular inhibition with the 3cl Protease, with inhibition of translation of the polyprotein processing and cleavage into viral RNA(32),(33).

Molecular Inhibition of the 3cl Protease with the complex 11a and 11b(31),(32) is crucial, Inhibition at small molecular inhibition can inhibit the viral genome complex to replicate ,by inhibiting the transcription of viral polyprotein processing (31),(32).

Overall Conclusion-

Hesperidin has high molecular inhibition with the nsp3 protein (nsp3) (26), can inhibit consequently the viral polyprotein (27),(28) processing, and crucial part in the viral replication (27),(28).

This could therefore lead to better therapeutic drugs for SARS-Cov-2 for 3cl Protease inhibition .

Kaempferol inhibits RDRP and 3cl Protease or Mpro Protease , which inhibits viral replication (29),(30) and viral transcription (29),(30),(31),(32),(33) and the central polymerase(29) (30),(31) and viral polyprotein processing (30),(31) .

Molecular Interactions of Kaempferol with Mpro Protease and RDRP can give realistic understanding of molecular Interactions of polyphenols such as Kaempferol with 3cl Protease and RDRP which could lead to further insight .

Epigallocatechin inhibits Plpro(Papain like Protease) which is a crucial for viral polyprotein processing and cleavage (27),(28),(29).

These results show that Epigallocatechin would a suitable candidate for combatting SARS-Cov-2.

Quercetin inhibits the 3cl Protease which is significant for viral translation and polyprotein processing (32),(33),(31).

Thereby Quercetin ,Epigallocatechin,Hesperidin and Kaempferol are vital candidates for inhibition of SARS-Cov-2 ,which could lead to potential pivotal roles in insights in molecular Interactions with SARS-Cov-2 .

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