Kuwanons, Promising inhibitors against the ACE-2, main protease of SARS-CoV-2 and falcipan-2 using molecular docking

Kamlesh Kumari

Deen Dayal Upadhyaya College, University of Delhi

Durgseh Kumar

Atma Ram Sanatan Dharma College, University of Delhi

Ramappa Venkatesh Kumar

Department of Zoology, Babasaheb Bhimrao Ambedkar University, Lucknow, UP, India

Prashant Singh (✉ psingh@arsd.du.ac.in)

Atma Ram Sanatan Dharma College, University of Delhi <https://orcid.org/0000-0001-9648-2275>

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Abstract

In the present scenario, the COVID-19 has affected the nations throughout the world. Till date, neither a vaccine nor a potential medicine is available for the cure from SARS-CoV-2 infection. Main protease of SARS-CoV-2 is responsible for the replication and transcription. Further, this virus binds to the angiotensin converting enzyme-2 (ACE-2) so there is need to find molecule, to avoid the binding of novel virus to ACE-2. It is reported that the molecules binds to falcipan-2 can help in the reduction of infection due to SARS-CoV-2. Therefore, there is a need to find promising candidate against the receptors, spread COVID-19. In the present work, kuwanons are proposed to be promising candidates against the main protease of SARS-CoV-2, ACE-2 and falcipan-2. The interaction between the different kuwanons with different receptors has been studied using the binding energy. Kuwanon M was found to best inhibitor against the main protease of SARS-CoV-2 and ACE-2. Further, the drug-likeness properties of all the 16 kuwanons were studied. Kuwanon-M found to be best inhibitor against the ACE-2 and main protease of SARS-CoV-2 with binding energy of -165.349 and -149.952 kcal/mol respectively while kuwanon-G found out to promising against the falcipan-2 with a binding energy of -149.573 kcal/mol.

Introduction

Since the prehistoric period, a major chunk of the world's population is well aware of the benefits of plant-based healthcare products due to their outstanding therapeutic properties. Further, the same attitude has been magnified among people to build strong immunity from plant sources. Most of the underexploited plants have become known to the world due to the profound impact of the folk medicine system and the modern research quest of many scientists. Among the underutilized plants, mulberry is considered as one of the most medicinally important plants, as it contains abundant natural compounds with proven therapeutic properties.(Kimura, Okuda et al. 1986; Liu, Li et al. 2016; Cakiroglu, Dervisoglu et al. 2020; Elbeaino, Incerti et al. 2020; Han, Song et al. 2020; Tam, Nam et al. 2020) Mulberry (*Morus spp*) is a perennial and multipurpose plant with high biomass production. It is mainly raised for silkworm rearing (*Bombyx mori*), which utilizes its leaves as their single food source to produce cocoons. Various parts of the mulberry plant have paramount significance for humans due to the presence of natural compounds such as flavonoids, polyphenols, alkaloids, terpenoids, steroids, and anthocyanins resveratrol, quercetin rutin, deoxynojirimycin (DNJ).(Nomura and Fukai 1981; Nomura, Hano et al. 2009; Akande, Falade et al. 2020; Arraki, Totoson et al. 2020; Gao, Zhang et al. 2020; Liu, Yan et al. 2020) In addition to the aforementioned bioactive phytochemicals, mulberry is also a rich source of Kuwanons.(Ramappa, Srivastava et al. 2020) Kuwanons are the natural isoprenylated flavonoids considered to be formed via an enzymatic Diels-Alder type reaction between an isoprenyl portion of an isoprenylphenol as the diene and a, b-double bond of chalcone as the dienophile. Different types of Kuwanons have been reported from mulberry plants such as Kuwanon S, G, T, H, L (root bark), Kuwanon X (leaves), Kuwanon C (root). It has been revealed through various studies that Kuwanons exhibit a great diversity of biological activities including antiviral, antibacterial, *tyrosinase inhibitory*, antioxidant and anti-inflammatory activity.(Park, You et al. 2003; Jung, Kang et al. 2014; Esposito, Tintori et al. 2015; Kong, Park et al. 2015; Gao, Han et al.

2016; Guo, Xu et al. 2016; Liu, Zhang et al. 2018) Despite their incredible pharmacological properties, Kuwanons have not been exploited significantly for human health enhancement.(Mihara, Hara et al. 1995; Gao, Han et al. 2016; Hu, Zheng et al. 2016; Koirala, Seong et al. 2018) Therefore, the current study is a systematic effort to reveal the potentiality and multifaceted uses of Kuwanons. Molecular docking is an interesting and promising approach to find the potential inhibitors against the receptors of interest in the form of binding energy.(Bassetto, De Burghgraeve et al. 2013; Dawood, Zarina et al. 2014; Burley, Berman et al. 2018; Abbad, Perera et al. 2019) The authors have used PDB ID of 1R42 and it is a native human angiotensin converting enzyme-related carboxypeptidase. It is containing 805 amino-acids and human ACE2 has the receptor for the attack of the spike protein of SARS-CoV-2. Further, another pdb having ID of 6LU7 is taken for the study and it is for the main protease of SARS-CoV-2. It is responsible for the infection in the respiratory system. Further, the PDB ID-2GHU is taken to study the activity against the falcipan-2. In the present work, kuwanons are explored for their potential in different biological potency against the main protease of SARS-CoV-2, angiotensin converting enzyme-2 and falcipan-2 using computational tools.

Experimental

Designing of the kuwanons All the kuwanon were drawn using chemdraw as in **Figure S1**.

Molecular docking

Structures of different kuwanons is drawn using Chemdraw and were optimized using gaussain 9.0 for further studies. For molecular docking, the protein data bank (PDB) files for main protease of SARS-CoV-2, falcipan-2 and angiotensin converting enzyme-2 were taken from RCSB.(Goodsell, Zardecki et al. 2019) They were prepared using Chimera for the molecular docking.(Pettersen, Goddard et al. 2004) Molecular docking of the 16 kuwanons was performed against main protease of SARS-CoV-2, falcipan-2 and angiotensin converting enzyme-2 was performed using iGemdock. It is a reliable computational tool to understand the binding of the small molecules with the receptors in the form of physical parameters i.e. binding energy.(Kumari, Singh et al. 2017; Vishvakarma, Patel et al. 2017; Vishvakarma, Singh et al. 2017; Kumar, Singh et al. 2019; Vishvakarma, Shukla et al. 2019; Vishvakarma, Singh et al. 2019; Kumar, Kumari et al. 2020; Kumar, Kumari et al. 2020; Kumar, Kumari et al. 2020; Vishvakarma, Kumari et al. 2020) This binding energy is due to contribution by the hydrogen bonding, van der Waal's and electrostatic interaction between the amino-acids of the receptor and the small molecules.(Hsu, Chen et al. 2011) The visualization of the interaction was studied using Discovery Studio Visualizer.

Drug-likeness

It is very important to know the drug likeness properties of the designed kuwanons and determined through SWISADME, an online web-server. It provides several informations like LogP, and number of violation for different drug likeness system, like lipinski's rule of five, vaber's rule etc.(Lohidashan, Rajan et al. 2018)

Results And Discussion

Molecular docking

Kuwanons are explored for their potential in different biological potency against the main protease of SARS-CoV-2, angiotensin converting enzyme-2 and falcipan-2 using iGemDock.(Vishvakarma, Kumari et al. 2015; Chakravarty, Singh et al. 2016; Singh, Kumari et al. 2016; Singh, Kumari et al. 2016; Singh, Kumari et al. 2016; Singh, Kumari et al. 2016) The binding energy of the kuwanons based on docking angiotensin converting enzyme-2, falcipan-2 and main protease of SARS-CoV-2 is given in **Table 1**. (Kumar, Kumari et al. 2020; Kumar, Kumari et al. 2020)

Table 1 Binding energies of the kuwanons based on docking angiotensin converting enzyme-2, falcipan-2 and main protease of SARS-CoV-2

C. No.	Binding energy with angiotensin converting enzyme-2	Binding Energy with falcipan-2	B.E. against main protease of SARS-CoV-2
A	-99.3526	-106.155	-125.345
C	-109.516	-108.908	-105.293
D	-97.307	-99.4465	-101.394
E	-116.568	-109.86	-116.189
F	-118.384	-102.792	-107.511
G	-145.572	-149.573	-125.95
H	-137.865	-134.123	-127.33
J	-137.662	-130.806	-123.673
K	-143.382	-147.87	-140.915
L	-153.195	-135.382	-147.092
M	-165.349	-131.544	-149.952
Q	-145.354	-142.868	-135.106
S	-124.794	-92.971	-120.015
T	-104.934	-106.189	-120.533
X	-134.4	-125.525	-124.863
Y	-130.111	-133.054	-122.297

Based on **Table 1**, it is clear that the kuwanons have the potential to inhibit the ACE-2, falcipan-2 and main protease of SARS-CoV-2. Kuwanon-M found to be best inhibitor against the ACE-2 and main protease of SARS-CoV-2 with binding energy of -165.349 and -149.952 kcal/mol respectively while kuwanon-G found out to promising against the falcipan-2 with a binding energy of -149.573 kcal/mol. The interaction of the best four kuwanons against the ACE-2, falcipan-2 and main protease of SARS-CoV-2 is given in Figure 2. .

The designed kuwanons hydrogen bonding as well non-hydrogen bonding i.e. pi interaction with the amino-acids of the ACE-2, falcipan-2 and main protease of SARS-CoV-2 as in **Figure 1**. Based on **Table 2**, Kuwanon M showed pi interaction with the HIS378, ALA348 TRP349, SER47, MET62, SER43 with distance of 6.86, 4.73, 4.19/5.75/6.15, 4.35, 6.42, 4.69 Å respectively while showed hydrogen bonding with PHE40, SER44, SER43, ASN51 haiving distance of 2.90, 2.94, 3.65, 4.87 Å respectively.

Table 2 Interaction of the best four kuwanons with the ACE-2

C. No.	Π Interactions		H. Bond Interactions	
	Interacted residue	Distance (Å)	Interacted residue	Distance (Å)
M	HIS378, ALA348, TRP349, SER47, MET62, SER43	6.86, 4.73, 4.19/5.75/6.15, 4.35, 6.42, 4.69	PHE40, SER44, SER43, ASN51	2.90, 2.94, 3.65, 4.87
L	PHE40, HIS378, GLU402,	6.48, 4.53, 6.81	ARG393, TYR385, ALA348	4.56/3.62, 6.00, 4.60
G	HIS378, TYR385, ARG514, GLU402, ASN394, ARG393, PHE40, HIS401, ASP382, ALA348	5.63, 8.48, 5.83, 5.59, 4.60, 4.74, 5.52, 5.45, 7.09, 6.25	ALA348, ASP382, ASP350	1.73/2.33, 4.96, 3.32/2.45
Q	PHE40, ASP382, HIS401, HIS378, ALA348, GLU402, ARG514	5.98, 7.79, 4.69/5.10/3.41, 5.39, 6.29, 6.59, 6.96	HIS374, GLU402	4.99, 3.19/2.54

C. No.	ACE-2	C.No.	Falcipan-2	C.No.	Main protease of SARS-CoV-2
M		G		M	
L		K		L	
G		Q		K	
Q		L		Q	

Based on **Table 3**, kuwanon G forms pi interaction with ASN81, LEU172, LEU84, ALA175, CYS42 with distance of 7.74, 4.96, 5.65, 5.33, 7.10 Å respectively and forms hydrogen bonding with CYS80, GLY83, TRP43, CYS42, ALA175, HIE85 with distance of 4.73, 2.76, 5.91, 3.59, 3.76, 3.05/2.82/3.88 Å respectively.

Based on **Table 4**, Kuwanon M forms pi interaction with ALA70, LYS97, having distance of 4.34/4.45, 6.06/6.25, 6.95 Å respectively and forms hydrogen binding with VAL73, ASN72, GLN69, ASN119, GLY71, SER121, MET17, ALA70 having distance of 3.58, 3.78, 4.42, 4.43, 3.34, 3.84, 5.60/4.54, 4.19 Å respectively.

Table 3 Interaction of the best four kuwanons with the falcipan-2

C. No.	Π Interactions		H. Bond Interactions	
	Interacted residue	Distance (Å)	Interacted residue	Distance (Å)
G	ASN81, LEU172, LEU84, ALA175, CYS42	7.74, 4.96, 5.65, 5.33, 7.10	CYS80, GLY83, TRP43, CYS42, ALA175, HIE85	4.73, 2.76, 5.91, 3.59, 3.76, 3.05/2.82/3.88
K	ALA175, CYS42, TYR78, LEU84	6.58, 7.38/6.11, 4.78/6.24/3.93, 3.84	LEU172, GLY83, ASP234, SER149	6.16, 3.11, 3.99, 3.70
Q	CYS80, CYS42, ALA175, TRP45, HIS174	4.60, 6.70/5.33/5.14/4.94, 4.35, 5.70, 6.36	ASN81, GLN36, HIS174, CYS42	3.08, 6.25, 4.11, 4.24
L	PHE164	4.35	ILE163, HIS197, ASP165, GLU161, LYS160	4.13, 4.67, 5.39, 4.91, 4.80

Table 4 Interaction of the best four kuwanons with the main protease of SARS-CoV-2

C.No.	Π Interactions		H. Bond Interactions	
	Interacted residue	Distance (Å)	Interacted residue	Distance (Å)
M	ALA70, LYS97, TRP31	4.34/4.45, 6.06/6.25, 6.95	VAL73, ASN72, GLN69, ASN119, GLY71, SER121, MET17, ALA70	3.58, 3.78, 4.42, 4.43, 3.34, 3.84, 5.60/4.54, 4.19
L	MET49, HIS41, GLU166	7.49/7.34, 6.78, 4.38	THR25, GLN189, LEU141, GLU166, CYS145	3.78, 6.05, 4.58/5.20, 4.94, 4.17
K	MET165, CYS145, HIS41, MET49,	4.75, 5.61/7.64, 4.10/6.86, 6.44/5.89	GLN189, GLU166, THR190, GLN192, THR45, MET165	5.80, 3.54, 4.90/4.85, 3.81, 3.72, 4.29
Q	CYS145	4.95	ASN119, GLY143, SER144, HIS163, THR26	4.58, 3.40, 3.27, 5.33, 4.69

Drug likeness of the designed kuwanons

LogP_{o/w} is a popular chemical descriptor and tells about the hydrophobicity or the lipophilicity of the molecules. It is an important physiochemical property in the discovery of a drug. A number of computational tools are available to determine the LogP value and it is a partition coefficient between the n-octanol and the water system. Further, the skin permeability coefficient (K_p) is also important and it correlates between the molecular size and the permeability. It is considered that more the negative value of

the logK_p indicates higher the permeability of the molecule or compound for the skin. Actually, drug likeness evaluates the molecule ability to be as oral drug with the bioavailability or not. In most of the literature, the researchers have determined only the Lipinski's rule of five. But, one should not ignore other methods like Ghose (Amgen), Veber (GSK), Egan (Pharmacia) and Muegge (Bayer).

Drug likeness properties of the designed kuwanons are determined and given in **Table 5**. The promising candidate against the ACE-2 and main protease of SARS-CoV-2 is kuwanon-M. It has high LogP value means it is highly hydrophobic in nature and cannot be considered as oral drug. Further, the logK_p is high in negative indicates not to be skin permeable. While kuwanon G showed best inhibition against the falcipan-2 and it is less hydrophobic and more permeable than the kuwanon M. But the filtered or screened kuwanons (M/G) showed more violation in drug-likeness methods (Lipinski/ ghose/ veber/ egan.muegge) as in **Table 5**.

Table 5 Drug likeness properties of designed kuwanons as in **Figure 1**

C. No.	Log P _{o/w}	TPSA (Å ²)	Drug likeness (no. of violations)					GI absorption	Log K _p (skin permeation) cm/s
			Lipinski	Ghose	Veber	Egan	Muegge		
A	4.29	100.13	0	0	0	0	1	High	-4.95
C	4.54	111.13	0	0	0	0	1	Low	-4.50
D	3.54	96.22	0	0	0	0	0	High	-5.75
E	4.41	107.22	0	0	0	0	1	High	-4.66
F	4.16	96.22	0	0	0	0	1	High	-5.14
G	5.17	209.12	3	4	1	2	5	Low	-5.34
H	6.36	209.12	3	4	1	2	5	Low	-4.39
I	5.42	195.18	2	4	1	2	4	Low	-4.90
K	5.08	209.12	3	4	1	2	5	Low	-5.34
L	3.56	205.12	3	3	1	1	5	Low	-6.51
M	7.49	211.26	3	4	1	2	6	Low	-4.00
Q	5.76	175.75	2	4	1	2	4	Low	-4.55
S	4.96	90.90	0	1	0	0	1	High	-3.95
T	4.39	111.13	0	0	0	0	1	Low	-4.94
X	4.18	178.91	2	4	1	2	3	Low	-5.72
Y	4.16	178.91	2	4	1	2	3	Low	-5.72

Conclusion

Mulberry belongs to the genus morus and considered to be a rapid growing tree. Many aspects of mulberry are explored like feeding of animal, phytochemicals used in medicine, remediation of soils etc. Kuwanon are the phytochemicals and obtained from different sources like mulberry. They have shown various biological activities like antibacterial activity against various microorganisms, anti-tuberculosis, antiviral etc. Still the mulberry is not explored thoroughly for its different application. In the present work, 16 kuwanon molecules were designed and docked against the main protease of SARS-CoV-2, ACE-2 and falcipan-2. It is found that kuwanon M has shown promising role in the inhibition of the ACE-2 and main protease of SARS-CoV-2. Further, drug-likeness properties of the designed kuwanons are determined using an online web-server.

Declarations

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Figures

C. No.		ACE-2	C.No.	Falcipan-2	C.No.	Main protease of SARS-CoV-2
M	Interactions <div> <div>van der Waals</div> <div>Unfavorable Bump</div> <div>Conventional Hydrogen Bond</div> <div>Unfavorable Donor-Donor</div> <div>π-π Stacked</div> <div>π-π T-shaped</div> <div>Alkyl</div> </div>		M		M

Figure 1

View for the interaction of the of the best four kuwanons with the protease of angiotensin converting enzyme-2, falcipan-2 and main protease of SARS-CoV-2

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