Millet derived flavonoids as potential SARS-CoV-2 main protease inhibitors: A computational approach

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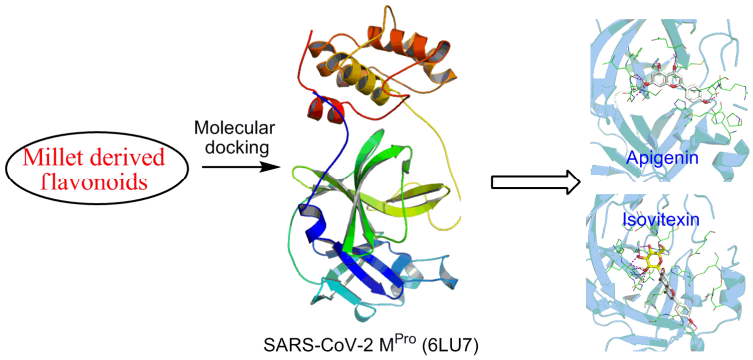
Graphical abstract



Abstract

The on-going pandemic COVID-19 has emerged as a major health threat across the globe. At present, antiviral drug discoveries are of great importance in combating the pandemic. Millets are known to contain numerous flavonoids with potential anti-viral properties. However, their anti-viral efficacy against SARS-CoV-2 is yet to be studied. The study uses the SARS-CoV-2 main protease (M^{pro}) as the potential anti-viral drug target and docks with eleven millet derived flavonoids taking HIV protease inhibiting drugs nelfinavir and saquinavir as control. AutoDock Vina was used for assessing the binding affinities and strength of bindings of flavonoids present in millet with the target protein M^{pro}. Further, the drug-likeness and pharmacokinetics properties of these flavonoids were also analyzed using admetSAR. The ADMET analysis showed that isoorientin, orientin, vitexin, meletin, catechin, and myricetin possess potential mutagenic property while daidzein could have a negative effect on reproductive system making these compounds as poor candidates for drug development against SARS-CoV-2. Based on the docking result on high binding affinities and positive ADMET properties, the present study infers that apigenin may be considered as a potential inhibitor of SARS-CoV-2 M^{pro} and may be further investigated to test its anti-viral activities using *in-vitro* and *in-vivo* study.

Keywords: Millets; Flavonoids; Nutraceuticals; SARS-CoV-2 M^{pro}; Molecular docking; Anti-viral agents

1. Introduction

Infectious diseases in general and respiratory tract infection and diarrhoeal diseases in particular are one of the leading causes of mortality and morbidity across the world [1]. The on-going pandemic of coronavirus disease 2019 (COVID-19) is linked with respiratory illness caused by SARS-CoV-2 virus and was reported in December 2019 [2]. The World Health Organization reports 9,129,146 confirmed cases resulted in 473,797 deaths with a fatality rate of 5.18 %, across the globe (as on 25th June 2020). Coronaviruses belong to family *Coronaviridae* [3] and are enveloped, large, and contain a single-stranded RNA genome that primarily causes enzootic infections in birds and mammals. The SARS-CoV-2 belongs to β-coronavirus group [4]. The incubation period ranges from 2 days to 14 days with the symptoms of cough, fatigue, myalgia, dyspnoea, and diarrhoea [5]. The corona viral genome mainly encodes four important structural proteins, viz., spike protein, nucleocapsid protein, membrane protein, and envelope protein. Among these, the entry of the virus into the host cells is mediated through spike proteins [4,6]. After entering into host cells, the viral genome gets translated and produces two large precursor polyproteins. Further, these polyproteins are cleaved into 16 mature non-structural proteins mediated by papain-like protease (PL^{pro}) and main protease or 3C-like protease (M^{pro}/ CL^{pro}). Moreover, many of the non-structural proteins play important roles in the replication of the viral genome and their transcription [7].

Presently, the non-availability of vaccine or antiviral drugs has doubled the threat making the situation highly troublesome [8]. To reduce the complicacies, various preventive as well as supportive therapies are being implemented [8,9]. To develop a therapeutic agent against SARS-CoV-2, screening the existing natural inhibitors is highly important. The present study aims to use the main protease M^{pro} as the potential anti-viral drug target due to the following reasons. First, M^{pro} of coronavirus has been studied extensively in the drug discovery [8,2,10]. Therefore, the structural as well as functional information related to this protein is available. Further, it has acted as a proven drug target for SARS-CoV [2], which shares the highest similarity with SARS-CoV-2, and also there is a prevalence of high sequence identity with the structural similarity of M^{pro} from SARS-CoV-2 with SARS-CoV M^{pro} as shown in Figure 1 . Second, $3CL^{pro}$ plays a key role in its self-maturation and the maturation of replicase enzymes and is known to inhibit the viral replication [11].

Literature on the use of natural products and medicinal plants as therapeutic against metabolic as well as infective diseases is more prevalent due to their minimal side effects [2,10,12]. In the context of the multiplication of viruses in the host body, it is evident that the

multiplication rate is known to be high when the immune system of the host is weak [13]. To strengthen the immune system, consumption of nutritious food is highly encouraged as nutrition plays a crucial role in the prevention of chronic diseases [14] when the essential nutrients act as nutraceuticals. The micronutrient content like minerals, vitamins, and presence of numerous secondary metabolites with strong anti-oxidant properties along with rich dietary fibre make millets an important functional food and nutraceuticals [15]. Further, millets contain several flavonoids like catechin, quercetin, luteolin, orientin, apigenin, isoorientin, vitexin, myricetin, isovitexin, daidzein, sponarin, violanthin, lucenin-1, and tricin; some of which have been demonstrated as effective anti-viral agents against swine fever virus and rotavirus [16-21]. However, the effect of these flavonoids on SARS-CoV-2 is scantly investigated. Thus, to breeze the conspicuous gap, this study attempts to explore the effectiveness of these flavonoids against SARS-CoV-2 using computational analysis.

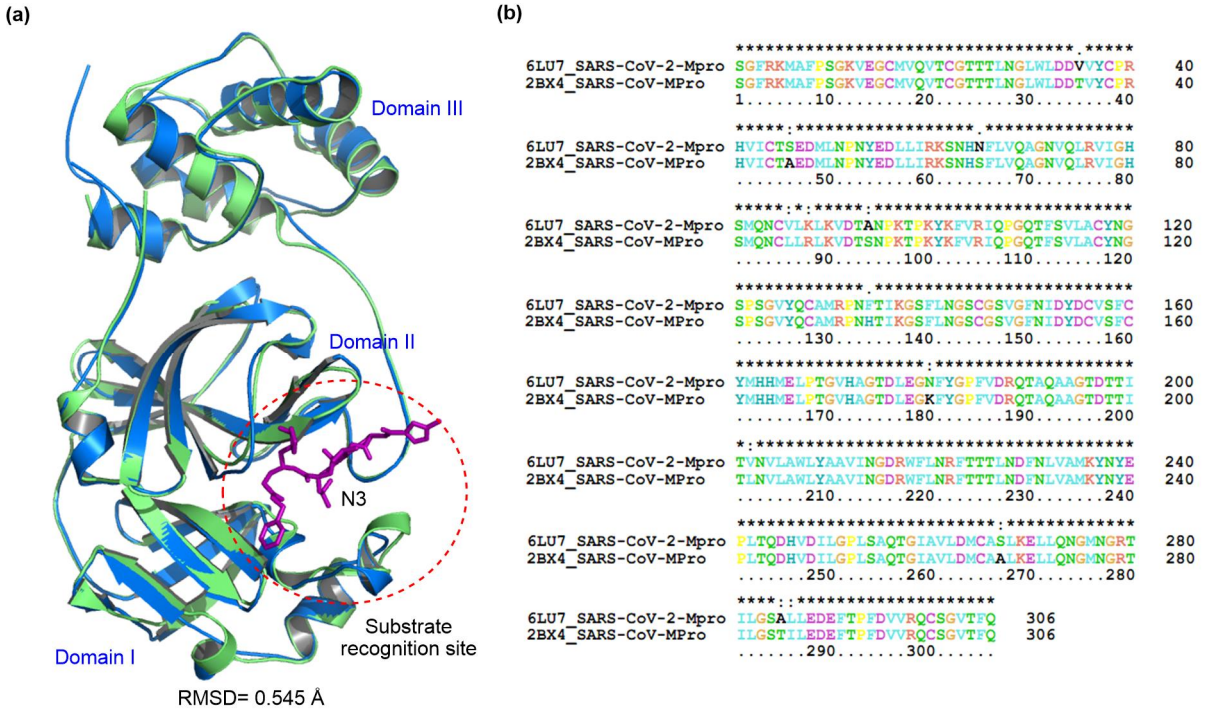


Figure 1: Schematic representation of main protease monomer (a) Superimposed structure of SARS-CoV-2 M^{pro} (PDB ID 6LU7) (marine blue) and SARS-CoV M^{pro} (PDB ID 2BX4) (lime green). SARS-CoV-2 M^{pro} comprises domain-I (residues 8-101), domain-II (residues 102-184), and domain-III (residues 201-303). Inhibitor N3 is in purple colour. (b) Sequence alignment of SARS-CoV-2 M^{pro} and SARS-CoV M^{pro}

2. Materials and methods

2.1. Molecular docking

Docking studies of different millet derived flavonoids with the SARS-CoV-2 main protease (M^{pro}) were carried out using AutoDock Vina [22]. HIV protease inhibiting drugs

nelfinavir and saquinavir were used as control. Three-dimensional structures of the ligands as well as the reference drugs were downloaded from the ZINC database (https://zinc.docking.org/) [23] in SDF format. Subsequently, all compounds were optimized with the Merck Molecular Force Field (MMFF94) [24] using PyRx [25]. The crystallographic structure of the SARS-CoV-2 M^{pro} with inhibitor N3 (PDB ID: 6LU7) [26] was retrieved from the protein data bank (http://www.rcsb.org/) [27] and processed before docking. During the process, polar hydrogen atoms and Kollman charges were added to the protein molecule. The active site residues were identified using ArgusLab (www.arguslab.com/arguslab.html). A search space around the active site was set to 25, 33, and 33 Å for x, y, and z dimensions, respectively, and centered at -15.52, -29.86, and 6.75 Å based on N3 binding site. The grid spacing was set to 1Å. To validate the docking protocol, first, inhibitor N3 was removed from the binding site of the main protease and re-docked using the same parameters and search space. The minimum energy conformation for each ligand was ranked according to the empirical scoring function. All protein-ligand complexes were analyzed and visualized with PyMol molecular graphics system (https://pymol.org/) [28]. LigPlot+ was used to infer interactions between the ligands and the protein [29].

2.2. Drug-likeness and toxicity analysis

Molinspiration property engine v.2018.10 (https://www.molinspiration.com/cgi-bin/properties) was used to predict properties like molecular weight, topological polar surface area (TPSA), LogP, hydrogen bond acceptors, and hydrogen bond donors to evaluate drug-likeness. ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties were calculated through admetSAR [30] and DataWarrior program [31]. Descriptors such as blood-brain barrier (BBB), human intestine absorption (HIA), cytochrome 450 inhibitor, aqueous solubility, mutagenicity, tumorigenicity, carcinogenicity, reproductive effect, and irritability were analysed for assessing ADMET properties. The above properties are essential in ascertaining the effect of the inhibitor to the human body, which affects and determines the performance of the ligand [32].

3. Results and discussion

3.1. Visualisation and analysis of docked structures

M^{pro} of SARS-CoV-2 was the preferred target because of its involvement in the viral replication and transcription. The substrate-binding site is located between domain-I and domain-II. The key residues involved in the substrate-binding are Thr24, Thr25, Thr26, His41,

Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His163, Met165, Glu166, His172, Asp187. Several flavonoids from millet were docked against the target to analyse the inhibitory activities and the molecular interactions within the binding site. The molecular docking results revealed that the identified millet flavonoids showed good binding affinities towards SARS-CoV-2 M^{pro} ranging from -8.1 to -7.2 kcal/mol. Saquinavir and nelfinavir (reference drugs) showed binding affinity of -8.5 and –7.7 kcal/mol respectively. When compared with inhibitor N3 (-7.7 kcal/mol), out of all flavonoids (considered in the study), isovitexin, isoorientin, apigenin, and orientin exhibited greater binding affinities. Among these, isovitexin (apigenin-6-C-glucoside) showed the highest binding affinity of -8.1 kcal/mol and formed ten hydrogen bonds with Thr24, Leu141, Gly143, Ser144, Cys145, and His163; whereas, Thr25, Thr26, Phe140, Asn142, Met165, and Glu166 were observed to form hydrophobic interactions (Figure 2a).

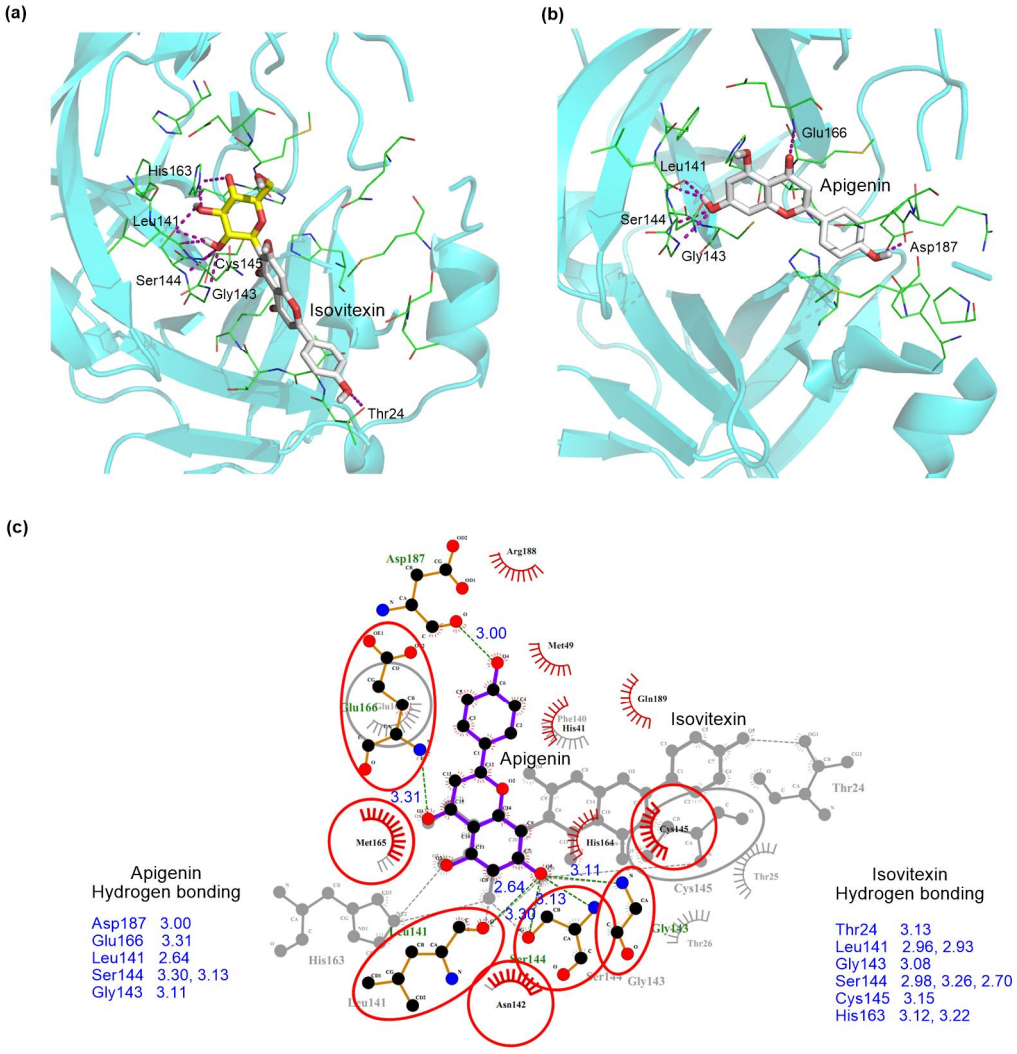


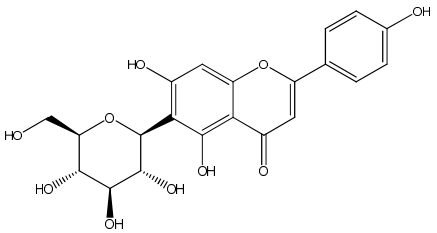
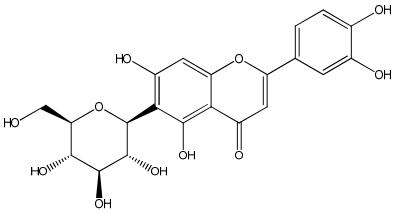
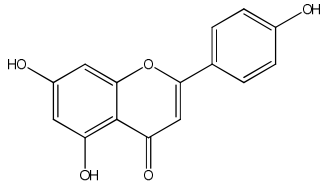
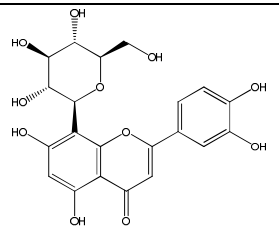
Figure 2: Pictorial representation of selected compounds from millet docked to the active site of SARS-CoV-2 M^{pro} (PDB ID 6LU7); (a) Isovitexin, (b) Apigenin, (c) Merged interaction plot of isovitexin and apigenin.

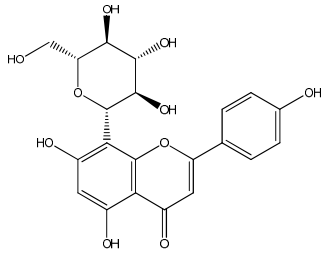
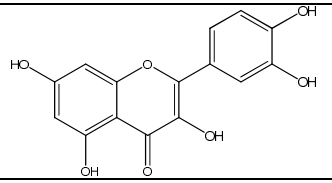
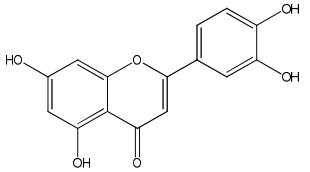
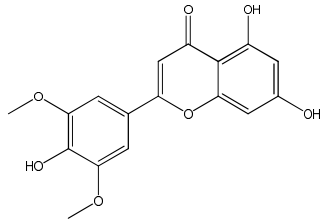
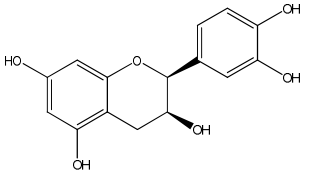
The binding affinity of isoorientin was found to be -7.9 Kcal/mol forming nine hydrogen bonds with Thr24, Thr45, Gly143, Cys145, Ser144, Leu141, and His163. Both apigenin and orientin showed the same binding energies of -7.8 kcal/mol (third highest) but they differed in forming their hydrogen bonds and interactions. Apigenin formed six hydrogen bonds with Asp187, Glu166, Leu141, Sr144, Gly143 showing hydrophobic interactions of Met165, Asn142, Cys145, His164, His41, Gln189, Met49, Arg188 (Figure 2b); whereas, orientin formed eight hydrogen bonds with Phe140, Gln189, Thr190, Gln192, Arg188, and Cys145 showing hydrophobic interactions of Glu166, Pro168, Met165, His164, His41. The comparative interaction plot of isovitexin and apigenin with M^{pro} shows better result for isovitexin (Figure 2c). The binding affinities and the molecular interactions of all the molecules with SARS-CoV-2 M^{pro} are depicted in Table 1.

3.2. Drug-likeness and ADMET analysis

In the drug development process, Lipinski *rule of five* and ADMET analysis plays a significant role as it explains the drug likeliness nature of the compounds [18]. As mentioned, blood-brain barrier, human intestine absorption, cytochrome 450 inhibitor, aqueous solubility, mutagenicity, tumorigenicity, carcinogencity, reproductive effect, and irritability properties of all the ligands were analyzed. Analysis of molecular properties showed that all compounds except isoorientin and orientin obeys Lipinski *rule of five* (Table 2). The ADMET result demonstrates that all the compounds analysed cannot cross BBB and has higher positive HIA. None of the compounds were found to be an inhibitor of cytochrome 450. However, the ADMET analysis indicates that flavonoids like isoorientin, orientin, vitexin, meletin, catechin, and myricetin were having mutagenic property and daidzein showed negative effect on the reproductive process. Hence, these compounds are poor candidates for drug development against SARS-CoV-2. Although luteolin and tricin do not show mutagenicity, tumorigenicity, negative reproductive effect, and irritability properties, these compounds are not suitable for anti-viral drug development owing to their poor binding energies with M^{pro} (Table 3). Thus, in a nutshell, it is articulated from the ADMET result that only two compounds (isovitexin and apigenin) may be considered further as a drug candidate against SARS-CoV-2. Moreover, out of the two compounds, the TPSA value of isovitexin was found to be above 140, which may affect the membrane permeability of the molecule [18]. Thus, apigenin was the only compound fulfilling all ADMET properties and may be used as an anti-viral agent against SARS-CoV-2.

Table 1: Binding energy of millet derived flavonoid against SARS-CoV-2 M^{Pro}

Compound	Binding affinity (kcal/mol) with SARS-CoV-2 M^{Pro}	Residues involved in H-bond	H-bond distance (Å)	Hydrophobic interactions	Phytochemical structure
Isovitexin	-8.1	Thr24 Leu141 Gly143 Ser144 Cys145 His163	3.13 2.96, 2.93 3.08 2.98, 3.26, 2.70 3.15 3.12, 3.22	Thr25, Thr26, Phe140, Asn142, Met165, Glu166	
Isoorientin	-7.9	Thr24 Thr45 Gly143 Cys145 Ser144 Leu141 His163	3.30, 2.86 3.27 2.94 3.31 3.05 2.79, 2.52 3.13	Thr25, Leu27, Met165, Phe140, Asn142, Glu166	
Apigenin	-7.8	Asp187 Glu166 Leu141 Ser144 Gly143	3.00 3.31 2.64 3.30, 3.13 3.11	Met165, Asn142, Cys145, His164, His41, Gln189, Met49, Arg188	
Orientin	-7.8	Phe140 Gln189 Thr190 Gln192 Arg188 Cys145	2.97 3.14 3.21, 3.23, 2.58 2.74 2.76 3.26	Glu166, Pro168, Met165, His164, His41	

Vitexin	-7.6	Thr26 His163 Ser144 Leu141 Phe140 Glu166 Asn142	3.17 3.03 3.06 3.17 3.22 3.12 2.75	Gln189, Met165, His41, Gly143, His164	
Meletin (Quercetin)	-7.5	Gln189 Ser144 Leu141 His163	2.86 2.81 2.81 3.20	His41, Met49, Asp187, Glu166, Phe140, Met165, Cys145	
Luteolin	-7.4	Thr190 Asn142 Arg188 Gln192	2.77, 2.83, 3.32 2.95 2.77 3.06	Glu166, Gln189, His41, His164, Cys145, Met165	
Tricin	-7.4	Gly143 His163 Cys145 Ser144 Leu141	3.16 2.94 3.29 2.96, 3.15 2.76	His172, Phe140, Met165, Glu166, Arg188, Gln189, Asn142	
Catechin	-7.3	Ser144 Leu141 Gln189	2.87 2.95 2.74	Arg188, Met165, His164, Cys145, His163, Phe140, Glu166	

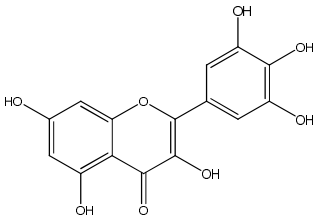
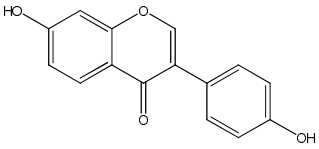
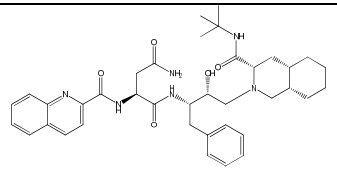
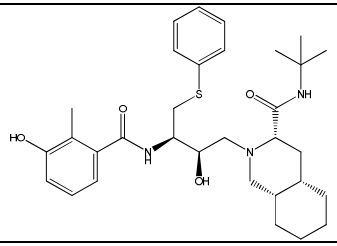
Myricetin		-7.3	Ser144 Leu141 His163 Arg188 Gly143 Cys145	2.82, 3.14, 2.96 2.81, 2.95 2.89 2.87 3.20 3,24	Asn142, Met165, Glu166, Gln189, Phe140	
Daidzein		-7.2	Phe140 Asp187	3.01 3.06	Asn142, Leu141, Gln189, Met165, Arg188, His164, His41, Cys145, His163	
Control (HIV protease inhibiting drugs)						
Saquinavir	Synthetic drug	-8.5	Tyr54 Asp187 Gln189 Asn142	3.18 3.27 3.14, 3.17 3.16	Leu141, Glu166, Met165, His41, Arg188, Met49, Thr26, Cys145, Leu27, Thr25, Gly143, Phe140	
Nelfinavir	Synthetic drug	-7.7	Glu166 Thr26	2.80 2.80	Met49, Asn142, Gly143, Thr25, His41, Gln189, His164, Met165, Arg188, Thr190	

Table 2: Molecular properties to predict drug likeliness of selective millet flavonoids

Compound	ZINC ID	Mol. Weight	TPSA	Log P	HB Acceptor	HB donor	No. of Violation	admetSAR prediction *
Isovitexin	ZINC4095704	432.38	181.04	0.52	10	7	1	In domain
Isoorientin	ZINC4349262	448.38	201.27	0.03	11	8	2	**Warning**
Apigenin	ZINC3871576	270.24	90.89	2.46	5	3	0	In domain
Orientin	ZINC4098560	448.38	201.27	0.03	11	8	2	**Warning**
Vitexin	ZINC4245684	432.38	181.04	0.52	10	7	1	In domain
Meletin	ZINC3869685	302.24	131.35	1.68	7	5	0	In domain
Luteolin	ZINC18185774	286.24	111.12	1.97	6	4	0	In domain
Tricin	ZINC5998961	330.29	109.36	2.30	7	3	0	In domain
Catechin	ZINC119978	290.27	110.37	1.37	6	5	0	In domain
Myricetin	ZINC3874317	318.24	151.58	1.39	8	6	1	In domain
Daidzein	ZINC18847034	254.24	70.67	2.56	4	2	0	In domain
Control (HIV protease inhibiting drugs)								
Saquinavir	ZINC3914596	670.86	166.75	4.26	7	5	1	In domain
Nelfinavir	ZINC3833846	567.80	101.89	5.47	6	4	1	In domain

TPSA- Topological polar surface area, HB acceptor- Hydrogen bond acceptor, HB donor- Hydrogen bond donor.

* admetSAR prediction description: http://lmmd.ecust.edu.cn/admetsar2/about/ad

Table 3: Pharmacokinetics and toxicity assessment of millet flavonoids

Compound	ZINC ID	BBB	HIA	CYP2D6 inhibitor	Aqueous solubility	Ames mutagenesis	Tumorigenic	Reproductive effects	Irritant
Isovitexin	ZINC4095704	-	+	-	-2.398	-	None	None	None
Isoorientin	**ZINC4349262**	-	+	-	-2.398	+	None	None	None
Apigenin	ZINC3871576	-	+	-	-2.777	-	None	None	None
Orientin	**ZINC4098560**	-	+	-	-2.398	+	None	None	None
Vitexin	**ZINC4245684**	-	+	-	-2.398	+	None	None	None
Meletin	**ZINC3869685**	-	+	-	-2.999	+	**High**	None	None
Luteolin	ZINC18185774	-	+	-	-2.999	-	None	None	None
Tricin	ZINC5998961	-	+	-	-3.289	-	None	None	None
Catechin	**ZINC119978**	-	+	-	-3.101	+	None	None	None
Myricetin	**ZINC3874317**	-	+	-	-2.999	+	None	None	None
Daidzein	**ZINC18847034**	-	+	-	-3.205	-	None	**High**	None
Control (HIV protease inhibiting drugs)									
Saquinavir	**ZINC3914596**	+	+	-	-3.225	-	None	None	None
Nelfinavir	ZINC3833846	-	+	-	-3.499	-	None	None	None

BBB: Blood-brain barrier, HIA: Human intestine absorption, CYP2D6: Cytochrome P450 2D6.

4. Conclusion

The present study investigated the potential inhibitors of SARS-CoV-2 considering millet derived flavonoids. The M^{pro} of SARS-CoV-2 was docked with eleven millet derived flavonoids, i.e., isovitexin, isoorientin, apigenin, orientin, vitexin, meletin, luteolin, and tricin, catechin, myricetin, and daidzein along with two reference drugs. Based on the high binding affinities and positive ADMET properties, the present study infers that apigenin may be considered as a potential inhibitor of SARS-CoV-2 M^{pro}. Intake of millets should be recommended to boost the immune system which can eventually effective towards covid-19. However, further extensive *in-vitro* and *in-vivo* studies need to be conducted to verify the anti-viral activity of apigenin.

Conflict of interest

There is no conflict of interest.

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