Molecular Docking Study of the Potential Relevance of the Natural Compounds Isoflavone and Myricetin to COVID-19

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Abstract: *The 2019 novel coronavirus (2019-nCoV) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly from its origin in Wuhan City, Hubei Province, China, to the rest of the world. The efficacy of herbal treatment in the control of contagious disease was demonstrated during the 2003 outbreak of severe acute respiratory syndrome (SARS). Natural compound used for this study were isoflavone and myricetin. Molecular docking was performed to analyze binding mode of the compounds towards 12 proteins related to COVID-19. The prediction shows that isoflavone and myricetin have moderate probability of antiviral activity. All of the docked compounds occupied the active sites of the proteins related to COVID-19. Based on QSAR and molecular docking, interactions were predicted with 10 out of 12 potential COVID-19 proteins for myricetin and with 9 out of 12 proteins interactions for isoflavone. A potential disease alleviating action is suggested for isoflavone and myricetin in the context of COVID-19 infection.*

Keywords: *SARS-CoV-2, Isoflavone, Myricitrin, Docking, QSAR.*

Introduction

The novel coronavirus (2019-nCoV) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly from its origin in Wuhan City, Hubei Province, China, to the rest of the world [29]. Till September 10, 2020 around 28,17,634 cases of coronavirus disease 2019 (COVID-19) and 910,610 deaths have been reported [30]. This pandemic is still

ongoing, so there is an immediate need to find effective preventive and therapeutic agents as soon as possible. Clinical symptoms of COVID-19 range from an asymptomatic state to acute respiratory distress syndrome and multi-organ dysfunction. In a subset of patients, the disease is progressing to pneumonia, respiratory failure, and death by the end of the first week. This development is associated with a severe increase in inflammatory cytokines, including IL7, IL2, IL10, IP10, GCSF, MIP1A, MCP1, and TNFα [2].

While specific vaccines and antiviral agents are the most effective methods for the prevention and treatment of viral infections, effective treatments targeting 2019-nCoV are not yet in place. The development of these treatments might take months or years, which means that faster treatment or control mechanisms should be established where possible. The efficacy of herbal treatment in the control of contagious disease was demonstrated during the 2003 outbreak of severe acute respiratory syndrome (SARS) [3]. A variety of small molecules, including such of natural origin, have been screened *in silico* and validated for their relevance to essential proteins in the coronavirus-induced SARS or Middle East Respiratory Syndrome (MERS) [23].

The natural compounds used in this study were isoflavone and myricetin. Isoflavones affect virus binding to cell membranes, cell entry, replication and virus protein translation inside the host cell, and formation of certain glycoprotein complexes of the virus envelope. At the host cell level, isoflavones can affect the activation of certain transcription factors and the secretion of cytokines, most of which have been attributed to reduced protein tyrosine kinase (PTK) activity. Inhibition of PTK activity decreased the entry of adenovirus, human herpesvirus 8 (HHV-8), Moloney murine leukemia virus (MoMLV), and simian vacuolating virus 40 (SV40) into host cells [11, 12, 19]. Whereas, myricetin was found to be a strong inhibitor of reverse transcriptase from human immunodeficiency virus (HIV) and Rauscher murine leukemia virus (RLV) [17]. Myricetin was reported to exhibit activity against SARS-CoV, a causative agent on the severe acute respiratory syndrome, and inhibited coronavirus helicase protein by affecting the function of adenosine triphosphatase (ATPase) [31].

Isoflavone and myricetin are natural compounds that have the potential for antiviral activity especially for COVID-19. Because of the rapid development of bioinformatics and chemioinformatics, preliminary screening was able to be performed *in silico* using QSAR and molecular docking. Molecular docking was performed to analyze binding mode of the compounds towards 12 proteins related SARS-CoV-2. Thus, this study aims to evaluate antiviral potential of the natural compounds isoflavone and myricetin especially through the possible antiviral activity against COVID-19 infection.

Materials and methods

Biological activity spectra prediction of isoflavone and myricetin (QSAR analysis)

Biological activity spectra of isoflavone and myricetin were predicted using PASS online which can be accessed through http://www.pharmaexpert.ru/PassOnline. PASS Online predicts over 4000 kinds of biological activity, including pharmacological effects, mechanisms of action, toxic and adverse effects, interaction with metabolic enzymes and transporters, and influence on gene expression. Simplified molecular-input line-entry system (SMILE) for every compound was used obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The resulted "Probability active" (Pa) and "Probability inactive" (Pi) estimations of antiviral potential were recorded. Pa estimates the chance that the studied compound is belonging to the sub-class of active compounds, while Pi estimates the chance that the studied compound is belonging to the sub-class of inactive compounds.

PASS online predicted the biological activity of query compound based on its structural similarity compared to the known active compound. Pa value was defined as probability for the query compound to be active for corresponding biological activity and vice versa for Pi. If Pa ≥ 0.9, the expected probability to find inactive compounds in the selected set was very low. If 0.5 < Pa < 0.7 the chance to find the activity in experiment was less, but the compound was not so similar to known pharmaceutical agents [7].

Binding affinity prediction of isoflavone and myricetin towards potential protein of COVID-19

The 3D structural data for every compound was obtained from PubChem database (https://pubchem.ncbi.nlm.nih.gov). Co-crystallized structures were obtained from RCSB database (https://rcsb.org). Crystal structure data was prepared by removing solvent and extracting bound ligand. AutoDock vina was used in molecular docking [27]. The docking simulation per each couple of compound and target protein were performed once generating one docking pose. This type of modelling is referred to as flexible docking. The docking methodology was validated by redocking the extracted bound ligand. Chimera was used on visualization in this study [20]. The list of protein used for binding affinity prediction can be seen at Table 1.

Table 1. List of protein used for binding mode and binding affinity prediction from PDB

Protein	Classification	PDB ID	Abbreviation
Angiotensin-converting enzyme 2	Antigen receptor	1R4L	ACE2
Transmembrane protease serine	Antigen receptor	2OQ5	TMPRSS
S protein subunit S2	Antigen receptor	6LXT	S2 su S protein
Nuclear factor kappa B	Cytokine pathway	1NFI	NFκ-B
Interleukin 6	Cytokine pathway	4CNI	IL6
Tumor Necrosis Factor alpha	Cytokine pathway	2AZ5	TNFα
Angiotensin 1 receptor	Cytokine pathway	6OS1	AT1R
Disintegrin	Cytokine pathway	3UCI	disintegrin
Metalloprotease 17	Cytokine pathway	2A8H	ADAM17
Interleukin 6 Receptor alpha chain	Cytokine pathway	1P9M	IL6Rα
GP130 protein	Cytokine pathway	1BQU	gp130
Signal transducer and activator of transcription 3	Cytokine pathway	6TLC	STAT3

The docking site follows the natural ligand position according to the protein listed in PDB access. The interaction assessment was carried out using the docking score and the number of hydrogen bond interactions (H-bonds interactions) between the target protein and the docked compound.

Building protein-protein network

The protein-protein interaction network of COVID-19 infection target to TMPRSS2 protein was built using STRING (http://string-db.org/). STRING builds networks for multiple proteins based on knowledge of text mining, experiments, co-expression, gene neighborhood, gene fusion, co-occurrence, and databases [26].

Results and discussion

The molecular docking method can be used to model the interaction between a small molecule and a protein at the atomic level, which helps to characterize the actions of small

molecules in the binding site of the target proteins as well as to elucidate fundamental biochemical processes [15]. In this study, PASS online shows that isoflavone and myricetin have antiviral properties. The biological activity prediction of these compounds showed various biological actions which can be seen from various Pa:Pi levels of antiviral activities. It can be observed that based on structural properties isoflavone have higher antiviral probability compared to myricetin (Table 2).

Table 2. Biological activity prediction

Compound	Pa	Pi	Activity
Isoflavone	0.690	0.006	Antiviral (Influenza)
Myricetin	0.519	0.004	Antiviral (Hepatitis B)

AutoDock Vina has favorable accuracy regarding the docking of flavonoid-conjugate. The molecular docking was performed to assess possible binding conformation of flavonoids conjugates towards receptor to gain possible biological actions of these compounds. The results of docking and hydrogen bond scores of isoflavone and myricetin are presented in Table 3. The final docking score and hydrogen bond interactions were mapped to a heatmap for comparison (Fig. 1).

Table 3. Predicted binding affinity and number of hydrogen bond interactions of isoflavone and myricetin with potential proteins relevant to COVID-19

Protein	PDB ID	Resolution	Isoflavone		Myricetin	
			Score	Hbond	Score	Hbond
ACE2	1R4L	3.00 Å	-7.4	7	-8.8	14
TMPRSS	2OQ5	1.61 Å	-2.3	2	121.7	3
S2 su S protein	6LXT	2.90 Å	-3.9	1	-3.5	13
NF-κB	1NFI	2.70 Å	-5.6	2	-6.7	40
IL6	4CNI	2.20 Å	-4.4	7	2.5	6
TNF-α	2AZ5	2.10 Å	NA	NA	NA	NA
Angiotensin 1 rec (AT1R)	6OS1	2.79 Å	NA	NA	NA	NA
disintegrin	3UCI	1.35 Å	-5.7	4	-5.7	20
metalloprotease 17 (ADAM17)	2A8H	2.30 Å	-8	6	-7.1	19
IL6Ra	1P9M	3.65 Å	-5.9	4	-5.9	19
gp130	1BQU	2.00 Å	NA	NA	-5.4	21
STAT3	6TLC	2.90 Å	-6.3	5	-6	8

Note: NA is no interaction characterized by the absence of hydrogen bonds between ligands and proteins

The use of these proteins is due to their correlation with SARS-CoV-2. The spike (S) protein of SARS-CoV-2, which plays a key role in the receptor recognition and cell membrane fusion process, is composed of two subunits, S1 and S2. The S1 subunit contains a receptor-binding domain that recognizes and binds to the host receptor angiotensin-converting enzyme 2, while the S2 subunit mediates viral cell membrane fusion by forming a six-helical bundle via the two-heptad repeat domain [9]. Meanwhile, ACE2 is a specific functional receptor for SARS-CoV [14]. The entry of SARS-COV2 into the human cell is initiated by transmembrane serine protease family members such as TMPRSS2, TMPRSS4,

TMPRSS11D, and TMPRSS11E. These serine proteases cleave and activate the spike protein. TMPRSS2 is present along with angiotensin-converting enzyme 2 (ACE-II) on the surface of the cell and acts as a receptor for SARS and SARS-CoV-2 [18]. Patients infected with COVID-19 have increased pro-inflammatory cytokines, such as IL-6 and TNF-α. Increased IL-6 and TNF-α can cause organ failure in several organs, such as the heart, lungs, kidneys and liver, which are severely damaged by cytokine storms [6]. SARS-CoV-induced acute respiratory distress syndrome (ARDS) in an animal model is prevented by inhibitors of angiotensin receptor type 1 (AT1R) [10]. AngII as a regulator pro-inflammatory cytokine via AT1R. The AngII-AT1R axis also activates NF-κB and disintegrin and metalloprotease 17 (ADAM17), which generates the mature form of epidermal growth factor receptor (EGFR) ligands and TNF-α, two NF-kB stimulators [5]. ADAM17 induction also processes the membrane form of IL-6Ra to the soluble form (sIL-6Ra), followed by the gp130-mediated activation of STAT3 via the sIL-6Ra-IL-6 complex in a variety of IL-6Ra-negative nonimmune cells including fibroblasts, endothelial cells, and epithelial cell. STAT3 is required for full activation of the NF-κB pathway, and the main stimulator of STAT3 *in vivo* is IL-6, especially during inflammation, although there are nine other members of IL-6 family cytokines that can activate STAT3 [16].

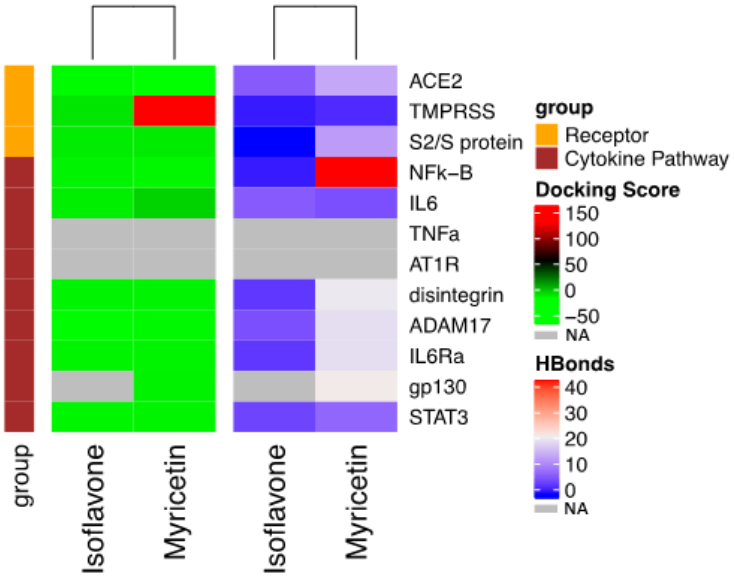

Fig. 1 Heatmap comparison of docking score and hydrogen bond between isoflavone and myricetin towards COVID-19 related proteins

In a previous research, 5,7,3′,4′-tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone has been successfully used as an anti-leishmanial agent [22]. According to [18], reporting on targeting of the SARS-CoV-2 3CLpro with isoflavone, the natural compound exhibited the highest binding affinity (−29.57 kcal/mol) and docking score S = −16.35, while myricetin had a binding affinity of −18.42 and docking score of S = −13.70.

Isoflavone showed interaction with all 3 receptors, both ACE2, TMPRSS, and S2/S proteins, Myricetin, however, although showing interactions with all 3 proteins, myricetin did not interact effectively with TMPRSS, which is evident from its positive docking score (121.7). It means that affinity is so low. The affinity is related to the free energy of Gibbs that docking affinity must be negative. However, in [21], myricetin has been reported to possess antiviral activity against HIV and influenza virus, and to inhibit helicase (nsp13), 3CL protease of SARS-CoV, reverse transcriptase, and protease enzymes.

Isoflavones and myricetin have no interactions with TNF-α and AT1R as proteins involved in cytokine signaling in COVID-19, whereas isoflavone also shows no interaction with the protein GP130 (gp130). Meanwhile, myricetin shows an effective interaction with the GP130 protein. Myricetin shows an effective interaction with NF-κB as shown in Table 3 having quite a lot of H-bonds (40) compared to other proteins. Poses and H-Bonds visualized using Chimera software, so that the poses presented in the figure match the scores reported.

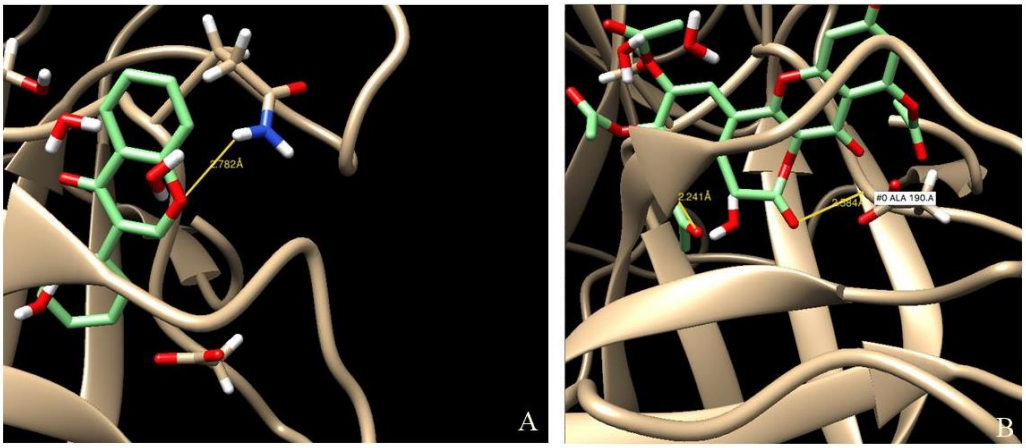

Fig. 2 The interactions between isoflavone (A) and myricetin (B) on TMPRSS protein

Fig. 3 shows the comparison of the interactions between isoflavone and myricetin on STAT3 protein. Isoflavone and myricetin can potentially bindSTAT3 protein, judging from their docking scores of −6.3 (isoflavone) and −6 (myricetin), and taking into account that both of these compounds have H-bonds. The binding mode of the compounds in STAT3 protein can be seen in Fig. 3. The binding mode of the isoflavone and myricetin can be seen in Fig. 4.

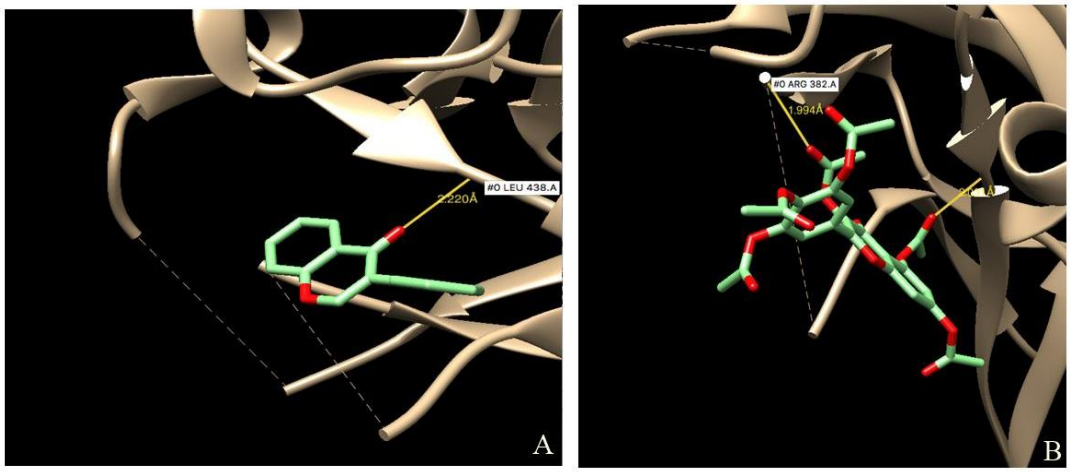

Fig. 3 Comparison of the interaction
between isoflavone (A) and myricetin (B) on STAT3 protein

Fig. 4 shows the comparison of the interactions between isoflavone and myricetin on ACE2. Isoflavone and myricetin can potentially bind ACE2 with a docking score of −7.4 (isoflavone) and -8.8 (myricetin). Fig. 5 shows the comparison of the interactions between isoflavone and myricetin on metalloprotease 17 (ADAM17) protein. Isoflavone and myricetin can potentially bind metalloprotease 17 (ADAM17) protein, judging from their docking scores of −8

(isoflavone) and −7.1 (myricetin), and taking into account that both of these compounds have H-bonds, isoflavone (6) and myricetin (19).

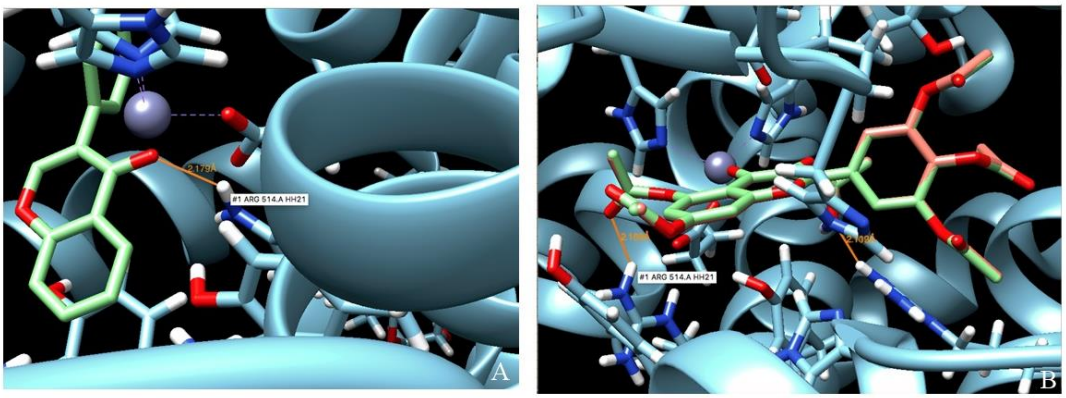

Fig. 4 Comparison of the interaction
between isoflavone (A) and myricetin (B) on ACE2 protein

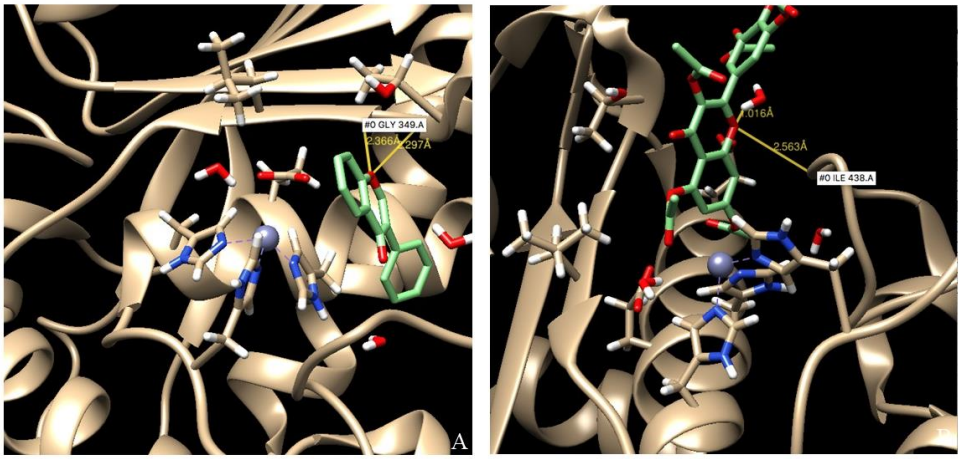

Fig. 5 Comparison of the interaction
between isoflavone (A) and myricetin (B) on ADAM17

The pathway of TMPRSS2 using STRING for known and predicted protein-protein network can be seen in Fig. 6A. In the pathway above it appears that TMPRSS2 activates the viral spike glycoproteins which facilitate virus-cell membrane fusions. TMPRSS2 facilitates human SARS coronavirus (SARS-CoV) infection, TMPRSS2 may be a relevant protease for lower-airway SARS-CoV infections [24]. Predicted functional partners of TMPRSS2 are Androgen receptor (AR), Transmembrane protease serine 4 (TMPRSS4), FAM3B protein, and Peptidyl-prolyl cis-trans isomerase FKBP5. While, predicted functional partners of ADAM17 are Tissue inhibitor of metalloproteinase 3 (TIMP3), Epidermal Growth Factor (EGF), Tumor Necrosis Factor (TNF), Neurogenic Locus Notch Homolog Protein-1 (NOTCH1), and Jagged-1 (JAG1)) as shown in Fig. 6B.

Several studies have discussed the potency of isoflavone and myricetin. At the host cell level, isoflavone can affect the induction of certain transcription factors and secretion of cytokines; most of these effects have been attributed to a reduction in PTK activity [4, 11, 12, 19]. Inhibition of PTK activity at later stages of virus infection has been reported to result in a decreased phosphorylation of herpes simplex virus-1 (HSV-1) polypeptides and bovine herpes virus-1 (BHV-1) glycoprotein E, resulting in a decreased overall virus replication [1, 32].

At the host cell level, isoflavone have also been shown to inhibit TNF-α secretion following infection [8, 25].

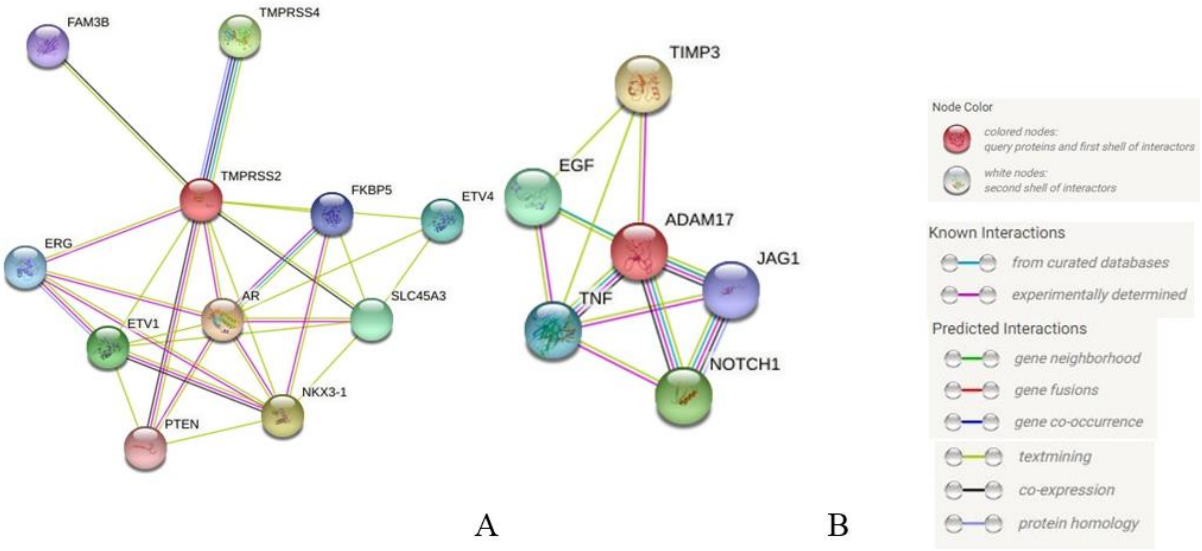

Fig. 6 Functionality based protein-protein network resulted using STRING: (A) TMPRSS2; (B) ADAM17

Myricetin has also been reported to have antiviral potential. According to Li et al. [13] myricetin possessed anti-HSV-1 and HSV-2 activities with very low toxicity, superior to the effects of acyclovir. Myricetin has been shown to block HSV infection through direct interaction with virus gD protein to interfere with virus adsorption and membrane fusion, which was different from the nucleoside analogues such as acyclovir. Myricetin has also been observed to down-regulate the cellular EGFR/PI3K/Akt signaling pathway to further inhibit HSV infection and its subsequent replication [13]. Considering the computer-aided predictions reported in the current study and the previously observed antiviral activities, isoflavone and myricetin were proposed as promising compounds that deserve further investigation of their potential therapeutic action on COVID-19. In this regard, in vitro and in vivo tests are necessary to determine the biological activities of isoflavone and myricetin.

Conclusion

The docking results of isoflavone and myricetin showed interactions with 10 out of 12 potential COVID-19 proteins for myricetin and with 9 out of 12 proteins for isoflavone. Therefore, potential disease-alleviating effects were suggested for these natural compounds regarding COVID-19. *In vitro* and *in vivo* experiments are necessary to validate the predicted mechanisms of action of isoflavone and myricetin.

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