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In silico molecular docking studies of certain commercially available flavonoids as effective antiviral agents against spike glycoprotein of SARS-CoV-2

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Abstract. – OBJECTIVE: Coronaviruses are large, enveloped, positive-stranded RNA viruses. These viruses contain spike-like projections of glycoprotein on their surface, which appear like a crown. Millions of infections and thousands of deaths have been reported worldwide to date. Hence, the objective of the present study was to look for *in silico* evaluation of certain commercially available flavonoids against SARS-CoV-2 enzyme.

MATERIALS AND METHODS: The *in silico* docking calculations were carried out using AutoDock 4.2 software. For the computational investigation, Apigenin, Catechin, Galangin, Luteolin, Naringenin were selected. An anti-viral drug Remdesivir was selected as reference drug.

RESULTS: In the present study we found that Naringenin showed excellent binding score with the SARS-CoV-2 enzyme compared to the reference drug and other selected flavonoids.

CONCLUSIONS: Based on the docking results, we conclude that Naringenin can be considered worthwhile to check its antiviral activity for the management of Coronavirus disease.

Key Words:
Binding energy, Docking interactions, Flavonoids, Inhibition constant.

Introduction

In early December 2019, the first novel corona virus outbreak appeared in Wuhan city, Hubei Province, China. It continues to spread at a rapid rate worldwide. Corona virus comes under the order Nidovirales and family coronaviridae and it is of four major genera: alpha, beta, gamma, delta corona virus. They are known as severe acute respiratory syndrome coronavirus, Middle-East respiratory syndrome, SARS-CoV-2[1]. In the field of molecular modelling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. AutoDock 4.2 is an automated procedure for predicting the interaction of ligands with bio macromolecular targets[2].

Flavonoids are a class of polyphenolic secondary metabolites found in plants. It has anti-inflammatory, anti-mutagenic and anti-carcinogenic properties coupled with its capacity to modulate key cellular enzyme functions[3,4]. For the present computational study flavonoids such as Apigenin, Catechin, Galangin, Luteolin, and Naringenin were selected based on their reported antiviral and drug likeness properties[5]. Therefore, the aim of this study was to look at the *in silico* evaluation of certain commercially available flavonoids against SARS-CoV-2 enzyme.

Materials and Methods

Software Used

Python 2.7 - language was downloaded from www.python.com, Cygwin (an information storage) c:\program and Python 2.5 were concurrently downloaded from www.cygwin.com; Molecular snap shots laboratory (MGL) equipment and AutoDock 4.2 were once downloaded from www.scripps.edu; Discovery studio visualizer 2.5.5 used to be downloaded from www.accelerys.com; ChemSketch was once downloaded from www.acdlabs.com. Online smiles translatory notation was once carried out the use of cactus.nci.nih.gov/translate/.

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Table I. Summary of the docking parameters of the flavonoids against SARS-CoV-2.

Name of the compound	Binding energy (kcal/mol)	Inhibition constant (μm)	Intermolecular energy (kcal/mol)
Apigenin	-7.17	5.56	-8.36
Catechin	-6.50	17.08	-8.29
Galangin	-5.69	67.56	-6.88
Luteolin	-7.22	5.07	-8.71
Naringenin	-7.29	4.50	-8.49
Remdesivir	-2.06	131.06	-5.13

Docking Methodology

The SARS-CoV-2 spike in prefusion state protein database has been downloaded from the RCSB protein data bank. The commercially available flavonoids such as Apigenin, Catechin, Galangin, Luteolin Naringenin and the standard drug Remdesivir have been constructed with the help of ChemSketch. The evaluation of drug-likeness test for the all the selected compounds was carried out using Molinspiration software[6].

The AutoDock 4.2 program was used to investigate ligand binding to structurally refined SARS-CoV-2 spike in prefusion state protein model using a grid spacing of 2.0 Å and the grid points in X, Y and Z axis were set to 90 X 90 X 90[7]. For each ligand, a docking stimulation was performed and the analysis was based on binding energies and inhibition constants and the molecules were then ranked in order of docking score[8].

Results

In Silico Cholinesterase Inhibitory Profiling

In silico SARS-CoV-2 spike protein inhibitory profiling was evaluated for certain commercially available flavonoids based on the binding energy, inhibition constant, intermolecular energy.

As shown in Table I, selected flavonoids exhibited excellent binding energy in the range from -7.29 kcal/mol to -5.69 kcal/mol against the target enzyme when compared to the standard (-2.06 kcal/mol). In the present study, it was observed that there is a decrease in the inhibition constant with a simultaneous reduction in the binding energy of the compound. All the selected flavonoids had showed constant attractive inhibition values in the range of 4.50 μM to 67.56 μM compared to the standard (131.06 μM). Reduction in the intermolecular energy of the compounds was noted with a progressive decline in binding energy. The selected compounds exhibited intermolecular electricity ranging from -8.49 to -6.88 when in contrast to the Remdesivir showed -5.13 against SARS-CoV-2 glycoprotein. The *in silico* research revealed that Naringenin was exhibited strong binding interactions and docking score which may emphasise that these compounds can be developed as potential leads for the management of SARS-CoV-2 disease.

The selected flavonoids showed optimal binding orientations against SARS-CoV-2 when compared with the standard. The interacting amino acid residues act as an essential role in inhibitory activity towards the target enzyme. The aminoacid residues responsible for the Naringenin (Figure 1) binding interaction with SARS-CoV-2 glyco-

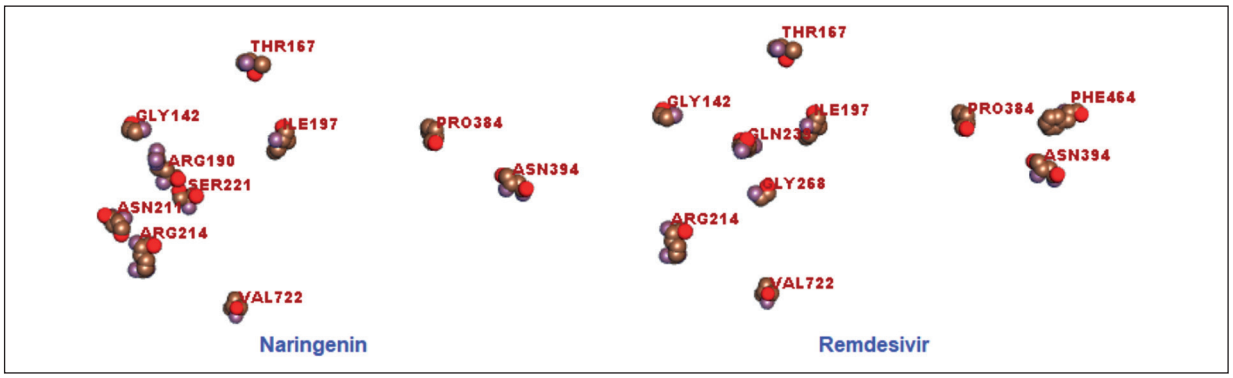

Figure 1. Binding orientations of SARS-CoV-2 spike in prefusion state protein with Naringenin and Remdesivir.

protein were GLY 142, THR 167, ARG 190, ILE 197, ARG 214, ASN 217, SER 221, PRO 384, ASN 394, VAL 722 and the for the Remdesivir (Figure 1) was found to be, GLY 142, THR 167, ILE 197, ARG 214, GLY 268, GLN 238, PRO 384, ASN 394, PHE 484, VAL 722. This result proves that the similar and effective binding orientations were present in the Naringein when compared with the standard Remdesivir. Based on the docking conformations, we predict that the interactions experienced with the Naringenin may lead to a potent inhibitor of the SARS-CoV-2 glycoprotein and thus act as a potent antiviral agent.

Discussion

At present, COVID-19 is scattering worldwide very fast and its control is very hard because there are no effective drugs available in markets. Joshi et al[9] conducted virtual screening of various phytochemicals to find novel compounds against the Coronavirus. Hence, they created 318 phytochemicals library from 11 different plants which have been reported as antibacterial, antiviral, and antifungal activity. The phytochemical library was focused into virtual screening against Angiotensin-Converting Enzyme 2 and Main protease (Mpro) targets. Top ten compounds were selected from each target which had significantly low docking energy as compared to the standard molecule[9].

Flavonoids, as phenolic compounds, have concerned considerable awareness due to their various pharmacological properties. Tutunchi et al[10] reviewed the promising effects and feasible mechanisms of action of naringenin against COVID-19. Apigenin was evaluated for its antiviral against HCV using host factor modulation technique. It resulted in reduction of mature miRNA122 production that is in harmony with HCV infection *in vitro*[11]. Luteolin has been hindered by the access of severe acute respiratory syndrome coronavirus (SARS-CoV) and influenza A virus by interfering with S2 protein of SARS-CoV viruses and hemagglutinins of influenza A virus[12].

Usually, natural compounds are known to have one or more medicinal properties. The independent descriptors were determined for selected natural compounds using Molinspiration software. A minimum of two violations are allowed to calculate the drug-likeness score. The different descriptors for each compound along with the standard drug were compared. All the selected commercially available flavonoids were shown no violations against Lipinski's rule.

We have identified potential SARS-CoV-2 protein inhibitors by targeting SARS-CoV-2 spyke protein model which is vital for survival of the Corona virus. Our *in silico* research revealed that Naringenin can be developed as a potential lead for the management of SARS-CoV-2 disease.

Conclusions

Naringenin showed excellent SARS-CoV-2 inhibiting properties in the *in silico* computational studies with remarkable docking score and orientation. Hence, the Naringenin was presented to the scientific community for further investigational confirmation for the development of potent SARS-CoV-2 inhibitor for the treatment of Corona disease.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS. J Virol 2020; 94: e00127-e00130.
2) Konc J, Penca T, Janezic M. Binding-sites prediction assisting protein-protein docking. Acta Chim Slov 2011; 58: 396-401.
3) Nautiyal S. Some medicinal plants of Garhwal hills-a traditional use. J Sci Res Plant Med 1981; 2: 12-18.
4) Srivasthava N, Rao S, Thosar A. Flavonoids: health booster. Int Res J Pharm 2012; 5: 142-146.
5) Seo DJ, Jeon SB, Oh H, Lee BH, Lee SY, Oh SH, Jung JY, Choi C. Comparison of the antiviral activity of flavonoids against murine norovirus and feline calicivirus. Food Control 2016; 60: 25-30.
6) Madeswaran A, Asokkumar K. Evaluation of inhibitory affinity potential of the alkaloids against crystal structure of human angiotensin-converting enzyme using Lamarckian genetic algorithm. Orient Pharm Exp Med 2015; 15: 183-189.
7) Prakhov ND, Chernorudskiy LA, Gainullin RM. VSDocker: a tool for parallel high-throughput virtual screening using AutoDock on Windows-based computer clusters. Bioinformatics 2010; 26: 1374-1375.

8) Madeswaran A. In silico screening of some commercially available alkaloids against angiotensin converting enzyme using Lamarckian genetic algorithm. Algerian J Nat Prod 2019; 7: 657-662.

9) Joshi T, Joshi T, Sharma P, Mathpal S, Pundir H, Bhatt V, Chandra S. In silico screening of natural compounds against COVID-19 by targeting Mpro and ACE2 using molecular docking. Eur Rev Med Pharmacol Sci 2020; 24: 4529-4536.

10) Tutunchi H, Naeini F, Ostadrahimi A, Hosseinzadeh-Attar JM. Naringenin, a flavanone with antiviral and anti-inflammatory effects: A promising treatment strategy against COVID-19. Phytother Res 2020; 34: 3137-3147.

11) Shibata C, Ohno M, Otsuka M, Kishikawa T, Goto K, Muroyama R, Kato N, Yoshikawa T, Takata A, Koike K. The flavonoid apigenin inhibits hepatitis C virus replication by decreasing mature microRNA122 levels. Virology 2014; 462-463: 42-48.

12) Yan H, Ma L, Wang H, Wu S, Huang H, Gu Z, Jiang J, Li Y. Luteolin decreases the yield of influenza A virus in vitro by interfering with the coat protein I complex expression. J Nat Med 2019; 73: 487-496.