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Molecular Docking Study of Different Natural Bio-Active Compounds of 'Swastha Kada Kashayam' on SARS-Cov-2 (Ncov) Proteins

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Keywords: Corona Kada Kashayam; Spick protein; COVID-19; Antiviral.

Abstract

Background: Since the COVID-19 a pandemic disease, so far there are no drugs or other treatment practices currently approved by the U.S. Food and Drug Administration (FDA) to treat COVID-19 patients. Current scenario is only clinical management includes infection prevention and control measures and supportive care, including oxygen supplementation and mechanical ventilator support when indicated. Researchers around the world are working on effective treatments and vaccines for the novel coronavirus disease known as COVID-19. Several pharmaceutical companies are working on many antiviral drugs, some of which are already in use against other illnesses, to treat people who already have COVID-19.

Methods: In the present study different natural bioactive compounds of swastha kada kashayam are docked against three different protein (PDB ID 6NUR (nCoV RdRP), PDB ID 6LZG (nCoV Spike), PDB ID - 6LUZ (nCoV Proteases) of SARS-CoV-2 using PubChem (CID-637358).

Results: In our findings, we observed that the negative binding energy reveals that the all the bioactive compounds selected for docking were capable of interacting with all the three proteins. The protein PDB ID 6NUR (nCoV RdRP) has a comparatively higher binding affinity to many of the active compounds than the other two proteins. Binding of EMA-Emblicanin A from Nelli was highest compared to others. Pedunculagin (PED) from Nelli showed the highest binding to PDB ID 6LZG (nCoV Spike) protein. EMA-Emblicanin A from Nelli showed the highest binding to PDB ID - 6LUZ (nCoV Proteases).

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Conclusion: Based on the analysis bioactive compounds from Nelli had shown the highest binding with all these proteins (6NUR, 6LZG and 6LU7). May be this two can be consider for treatment in alone (Mono therapy) or in combination with Manjal (Synergistic). Hence, Swastha Kada Kashayam have high antiviral against nCoV-2 and we conclude that this kashayam can be taken as prophylactic against covid-19.

Introduction

Globally, as of 1 June 2020, there have been 6,057,853 confirmed cases of COVID-19, including 371 to 166 deaths, reported to World Health Organization (WHO). Although most infections are self-limited, about 15% of infected adults develop severe pneumonia that requires treatment with supplemental oxygen and an additional 5% progress to critical illness with hypoxemic respiratory failure. Acute respiratory distress syndrome and multi organ failure that necessitates ventilator support, often for several weeks [1]. At least half of the patients with coronavirus disease 2019 (COVID-19) requiring invasive mechanical ventilation have died in hospital [2], and the associated burden on health-care systems, especially intensive care units, has been overwhelming in several affected countries. Although several approved drugs and investigational agents have shown antiviral activity against SARS-CoV-2 in vitro [3], at present there are no antiviral therapies of proven effectiveness in treating severely ill patients with COVID-19. No specific antiviral drug has been proven effective for treatment of patients with 2019-nCoV. AS the world excitedly waiting for a therapy for COVID-19 virus (SARS-CoV-2 (2019-nCoV), there have been several attempts in the recent weeks to ask if existing solutions and compounds could be repositioned to address the specter of COVID-19, if not as a curative, at least as a preventive.. However, many of these initiatives to examine the potential of several bioactive compounds in inhibiting the COVID-19 main active protein using molecular docking analysis to arrive at binding affinity. A recent study show that several plant secondary metabolites such as kaempferol, quercetin, luteolin-7- glucoside, de methoxide curcumin, naringenin, apigenin-7- glucoside, oleuropein, curcumin, catechin, and epicate- chin-gallate have the potential to inhibit the COVID-19 M^{Pro} protease. In a more recent paper, first released on 20 March 2020, by Zhang *et al*. report a potent ketoamide suggest that subject to further investigation, it could form an attractive drug candidate [4-6].

Bioinformatics is one of the most important and innovative approaches in the design and manufacturing of novel drugs. Due to the high cost of clinical and pre-clinical trials, are time consuming and the possibilities of errors, instead various bioinformatics techniques are now a days used in the development of new drugs. Molecular docking, simulation, target point determination and chemical stability studies are the most important bioinformatics methods used in the drug design.

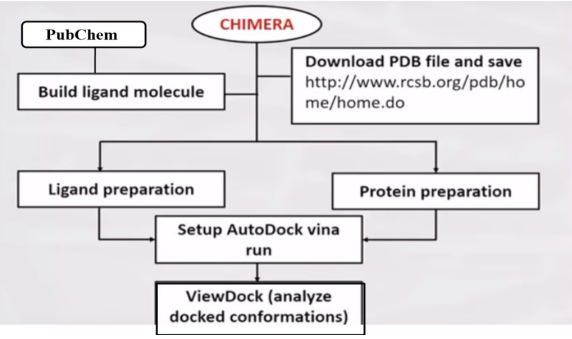
Molecular docking is a method, which predicts the preferred relative orientation of one molecule (key) when bound in an active site of another molecule (lock) to form a stable complex such that free energy of the overall system is minimized. It exploits the concept of molecular shape and physicochemical complementarity. One of the new therapeutic strategies for viral infection apart from the design and chemical synthesis of protease inhibitors is the search for inhibitors of this enzyme among natural compounds in order to obtain drugs with minimal side effects. The present study was undertaken to evaluate the effect of Swastha Kad Kasayam bioactive compounds, against COVID-19 protease using molecular docking study. Considering the fact that most of the natural product ligand chosen for the study is commonly used spices, and medicinal plants, it is likely that their eventual deployment as drug candidates could accelerate regulatory approvals. In the present study different natural bioactive compounds of swastha kada kashayam are docked against three different protein (PDB ID 6NUR (nCoV RdRP), PDB ID 6LZG (nCoV Spike), PDB ID - 6LUZ (nCoV Proteases) of SARS-CoV-2 using PubChem (CID-637358).

Methods

This is a pre-clinical observational study design. The study was carried out in the Tamil nadu Dr.MGR Medical University for a period of two months. Study trial drug swantha kada kashayam was used against nCoV-2. The major ingredients of the kashayam is Thippili, Piper nigrum, Manjal, Tulsi and Nelli. Bioactive compound of each ingredients of swastha kada kasayam were interlinked with three different proteins of nCoV2. The compounds to be docked are active compounds from plants products that have been known to have antiviral activities. In this study the interaction of biological compounds were described below. In order to get the structural compound of the nCoV, a Pub Chem database was used. The 3D structures of the selected ligands were obtained from the https://pubchem.ncbi.nlm.nih.gov/ as PDB files.

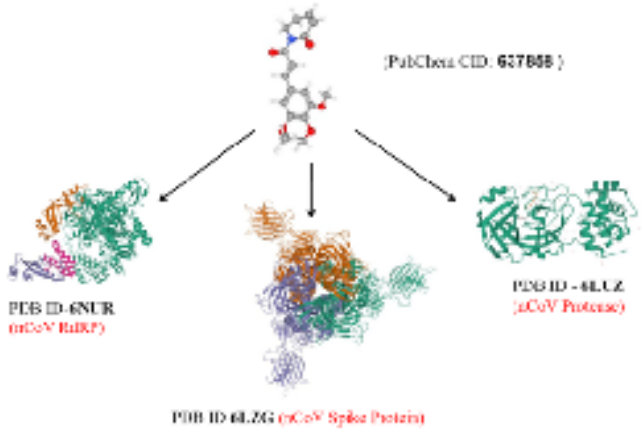
Molecular docking steps

Molecular Docking Steps



Determination of receptors

In the present study different natural bioactive compounds of swastha kada kashayam are docked against three different protein of SARS-CoV-2.



Ligand and receptor protein

Three-Dimensional (3D) structures Spike protein, RdRP, Protease protein of SARS-CoV-2 were retrieved from Protein Data Bank in .pdb formats. These proteins were served as receptors in docking process. Ligand structures were obtained from the PubChem site. The search was done by entering the name of the ligand in the search option. Each ligand's file was downloaded and saved. Files in the sdf format were converted to .pdb using Open Babel. The .pdb format ligand was opened using the Autodock Tools tool. Torque adjustment was done by detecting root and adjusted as desired. The file was saved in .pdbqt format.

Active site determination

The location of the amino acids as active sites in the receptor region where the ligand was docked was determined using Autodock Tools. For this reason, a three-dimensional map of the grid box was made in the receptor region where the ligand was docked. Determination of this map can be based on the type of docking used. A three-dimensional map was made as wide as the size of the receptor (Spike glycoprotein) itself so that the ligand was likely to be docked to all parts of the receptor (blind docking). In Mpro/3CLpro docking, the three dimensional map was only the size of the area to be docked (targeted docking).

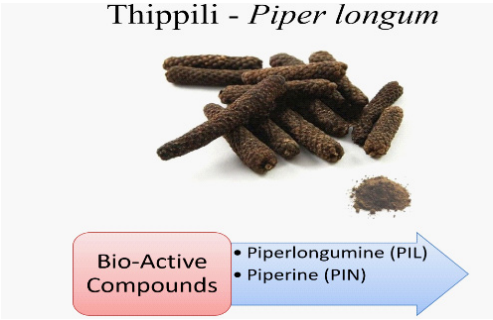
Analysis and visualization

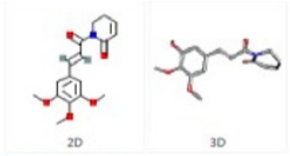
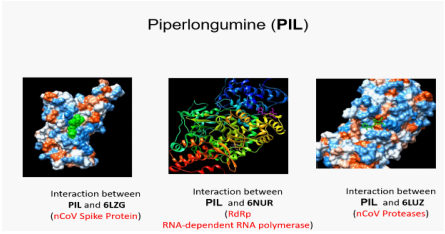
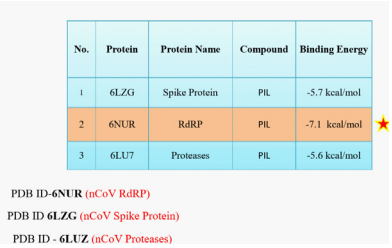
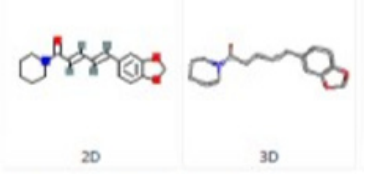
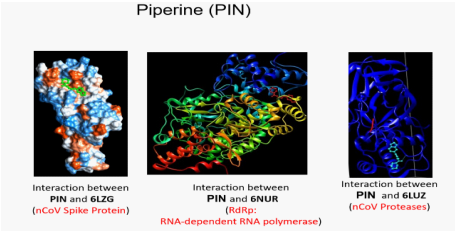
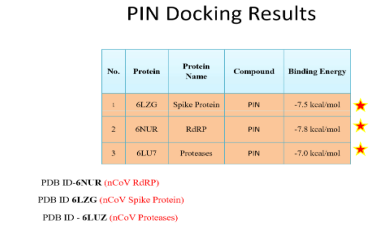
The results of the docking calculation were shown in the output in notepad format. Determination of the docking conformation of the ligand was done by selecting the pose with the highest affinity (most negative Gibbs free energy).

Results

The list of plants that have active compounds used as ligands is presented below. The estimation of free energies of binding between potential inhibitors and receptors was calculated using a docking experiment.

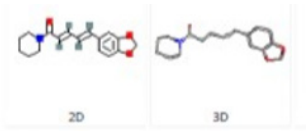
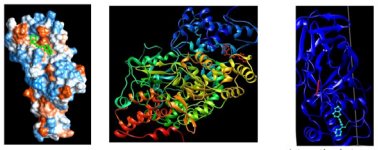
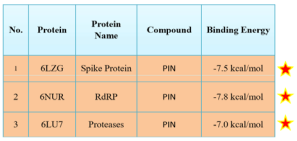
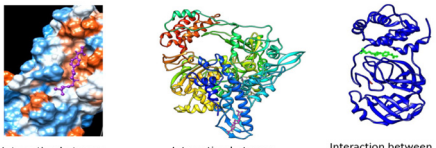
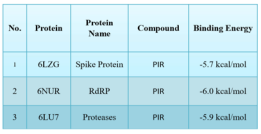
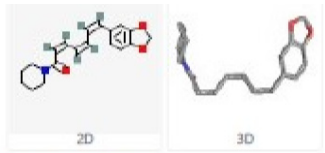
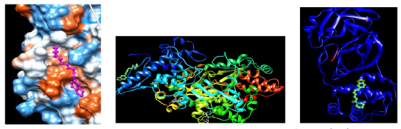
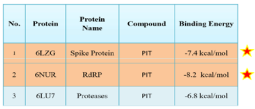
Table 1: Thippilli - Structure and docking results of the compounds



Natural product and structure of the active compound	Structure and binding capacity	Docking result
Piperlongumine 		
Piperine 		

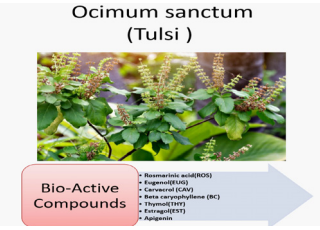
The negative binding energy reveals that the all the bioactive compounds selected for docking were capable of interacting with all the three proteins of nCoV-2. Interaction of Piperlongumine has a higher binding affinity with the RdRp protein compare to other viral proteins. In addition, the interaction between all the three viral proteins has higher binding energy with the piperin.

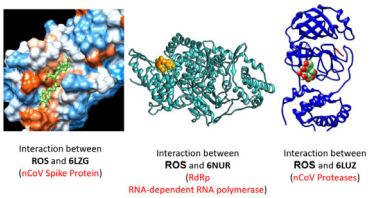
Table 2: Piper nigrum: Structure and docking results of the compounds.

Natural product and structure of the active compound	Structure and binding capacity	Docking result
Piperin 	Piperine (PIN)  Interaction between **PIN** and **6LZG** (nCoV Spike Protein) Interaction between **PIN** and **6NUR** (RdRp: RNA-dependent RNA polymerase) Interaction between **PIN** and **6LUZ** (nCoV Proteases)	PIN Docking Results 
Piperamide 	**Piperamide(PIR)**  Interaction between **PIR** and **6LZG** (nCoV Spike Protein) Interaction between **PIR**and **6NUR** (RdRp: RNA-dependent RNA polymerase) Interaction between **PIR** and **6LUZ** (nCoV Proteases)	PIR Docking Results 
Piperettine 	**Piperettine(PIT)**  Interaction between **PIT** and **6LZG** (nCoV Spike Protein) Interaction between **PIT**and **6NUR** (RdRp: RNA-dependent RNA polymerase) Interaction between **PIT** and **6LUZ** (nCoV Proteases)	PIT Docking Results 

All the three viral proteins had higher binding energy to the piperin bioactive compound of piper nigrum. The Spike protein and RdRp protein has higher binding energy to piperettine than the protease protein

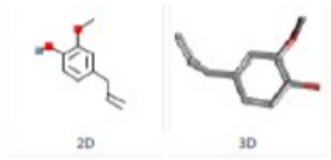
Table 3: Tulsi: Structure and docking results of the compounds.

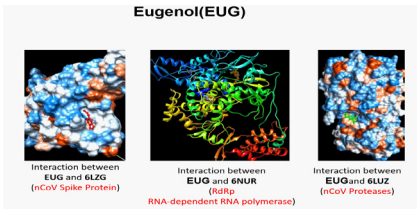


Natural product and structure of the active compound	Structure and binding capacity	Docking result
Rosmarinic acid 	**Rosmarinic acid (ROS)**  Interaction between **ROS** and **6LZG** (nCoV Spike Protein) Interaction between **ROS** and **6NUR** (RdRp RNA-dependent RNA polymerase) Interaction between **ROS** and **6LUZ** (nCoV Proteases)	ROS Docking Results

No.	Protein	Protein Name	Compound	Binding Energy
1	6LZG	Spike Protein	ROS	-7.5 kcal/mol
2	6NUR	RdRP	ROS	-7.4 kcal/mol
3	6LU7	Proteases	ROS	-7.2 kcal/mol

Eugenol

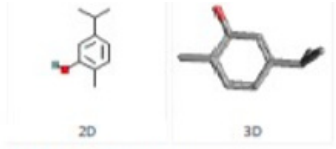


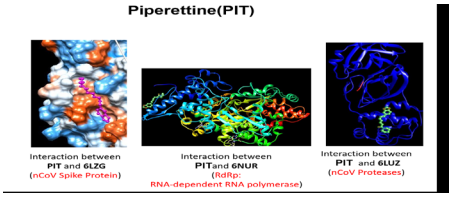


EUG Docking Results

No.	Protein	Protein Name	Compound	Binding Energy
1	6LZG	Spike Protein	EUG	-5.2 kcal/mol
2	6NUR	RdRP	EUG	-6.0 kcal/mol
3	6LU7	Proteases	EUG	-4.9 kcal/mol

Carvacrol

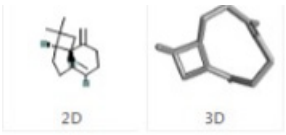


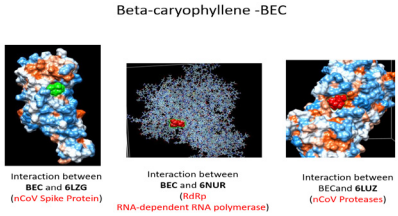


PIT Docking Results

No.	Protein	Protein Name	Compound	Bindin
1	6LZG	Spike Protein	PIT	-7.4 k
2	6NUR	RdRP	PIT	-8.2 k
3	6LU7	Proteases	PIT	-6.8 k

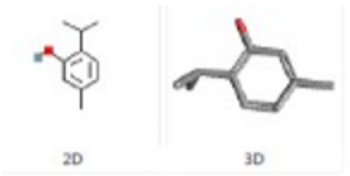
Beta caryophyliene



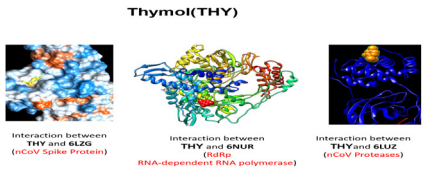


BEC Docking Results

No.	Protein	Protein Name	Compound	Binding Energy
1	6LZG	Spike Protein	BEC	-5.7 kcal/mol
2	6NUR	RdRP	BEC	-6.5 kcal/mol
3	6LU7	Proteases	BEC	-5.3 kcal/mol

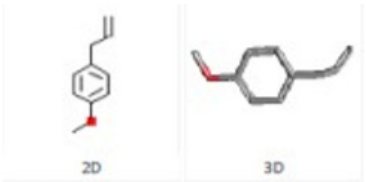


Thymol

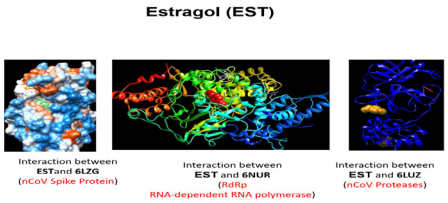


THY Docking Results

No.	Protein	Protein Name	Compound	Binding Energy
1	6LZG	Spike Protein	THY	-5.3 kcal/mol
2	6NUR	RdRP	THY	-5.8 kcal/mol
3	6LU7	Proteases	THY	-5.0 kcal/mol



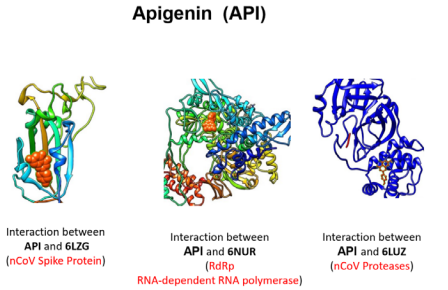
Estragol



EST Docking Results

No.	Protein	Protein Name	Compound	Binding Energy
1	6LZG	Spike Protein	EST	-4.8 kcal/mol
2	6NUR	RdRP	EST	-6.0 kcal/mol
3	6LU7	Proteases	EST	-4.6 kcal/mol

Apigenin

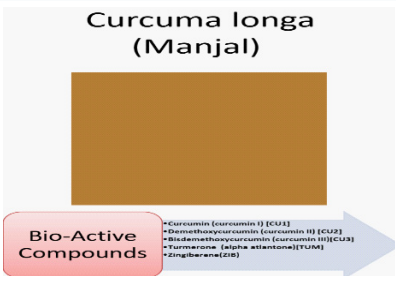


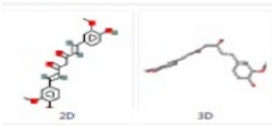
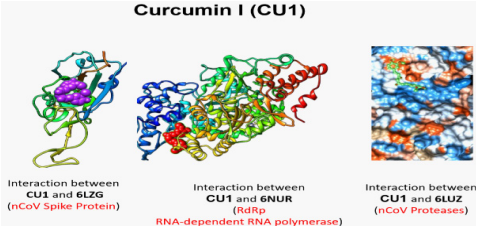
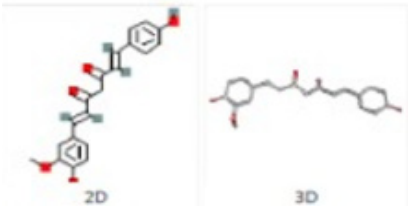
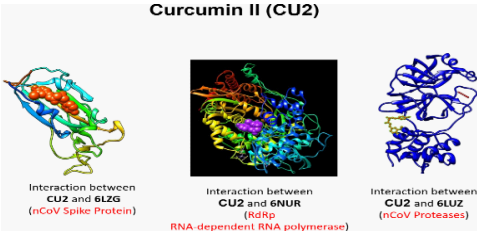
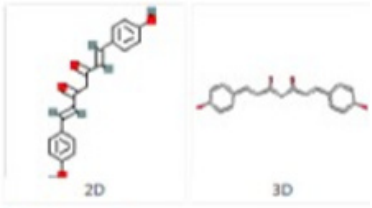
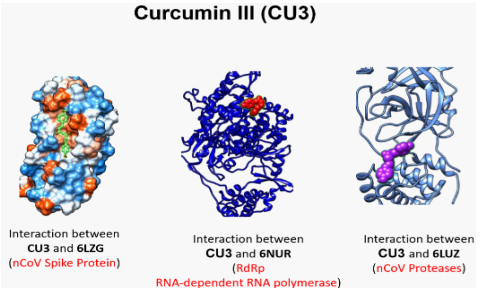
API Docking Results

No.	Protein	Protein Name	Compound	Binding Energy
1	6LZG	Spike Protein	API	-7.2 kcal/mol
2	6NUR	RdRP	API	-8.0 kcal/mol
3	6LU7	Proteases	API	-6.8 kcal/mol

All three proteins had higher binding affinity with the Rosemerinic acid of the bioactive compound of Tulsi and the other active compound present in Tulsi was Apigenin. The Spike protein and RdRp protein has higher binding energy to piperettine than the protease protein.

Table 4: Manjal: Structure and docking results of the compounds.



Natural product and structure of the active compound	Structure and binding capacity	Docking result
Curcumin acid 	**Curcumin I (CU1)**  Interaction between **CU1** and **6LZG** (nCoV Spike Protein) Interaction between **CU1** and **6NUR** (RdRp RNA-dependent RNA polymerase) Interaction between **CU1** and **6LUZ** (nCoV Proteases)	CU1 docking results
Curcumin II acid 	**Curcumin II (CU2)**  Interaction between **CU2** and **6LZG** (nCoV Spike Protein) Interaction between **CU2** and **6NUR** (RdRp RNA-dependent RNA polymerase) Interaction between **CU2** and **6LUZ** (nCoV Proteases)	CU2 Docking Results
	**Curcumin III (CU3)**  Interaction between **CU3** and **6LZG** (nCoV Spike Protein) Interaction between **CU3** and **6NUR** (RdRp RNA-dependent RNA polymerase) Interaction between **CU3** and **6LUZ** (nCoV Proteases)	CU3 Docking Results

No.	Protein	Protein Name	Compound	Binding Energy
1	6LZG	Spike Protein	CU1	-6.8 kcal/mol
2	6NUR	RdRP	CU1	-7.2 kcal/mol
3	6LU7	Proteases	CU1	-6.8 kcal/mol

No.	Protein	Protein Name	Compound	Binding Energy
1	6LZG	Spike Protein	CU2	-7.1 kcal/mol ★
2	6NUR	RdRP	CU2	-7.2 kcal/mol ★
3	6LU7	Proteases	CU2	-6.5 kcal/mol

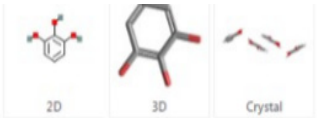
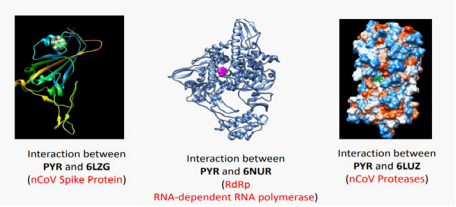
No.	Protein	Protein Name	Compound	Binding Energy
1	6LZG	Spike Protein	CU3	-7.2 kcal/mol
2	6NUR	RdRP	CU3	-7.0 kcal/mol
3	6LU7	Proteases	CU3	-7.0 kcal/mol

Onlu RdRp protein has a binding affinity with the active compound Curcumin-1 and Spike protein and RdRp had a higher binding affinity to the active compound Curcumin-2 but all the three proteins had higher binding affinity to curcumin-3.

Table 5: Nelli: Structure and docking results of the compounds.

Nelli - *Emblica officinalis*

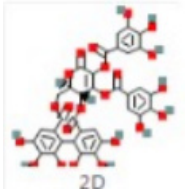
Bio-Active Compounds
- Pyrogallol (PYR)
- Emblicanin A (EMA)
- Emblicanin B (EMB)
- Puningluconin (PUN)
- Pedunculagin (PED)

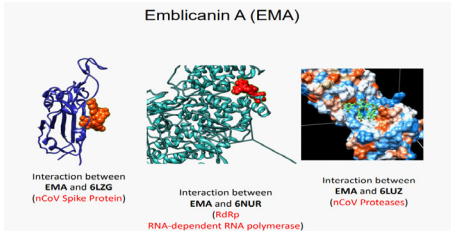
Natural product and structure of the active compound	Structure and binding capacity	Docking result
Pyrogallol 	Pyrogallol (PYR)  Interaction between **PYR** and **6LZG** (nCoV Spike Protein) Interaction between **PYR** and **6NUR** (RdRp RNA-dependent RNA polymerase) Interaction between **PYR** and **6LUZ** (nCoV Proteases)	PYR Docking Results

No.	Protein	Protein Name	Compound	Binding Energy
1	6LZG	Spike Protein	PYR	-5.5 kcal/mol
2	6NUR	RdRP	PYR	-5.5 kcal/mol
3	6LU7	Proteases	PYR	-4.8 kcal/mol

PDB ID-**6NUR** (nCoV RdRP)
PDB ID **6LZG** (nCoV Spike Protein)
PDB ID - **6LUZ** (nCoV Proteases)

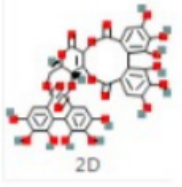
Emblicanin-A (EMA)

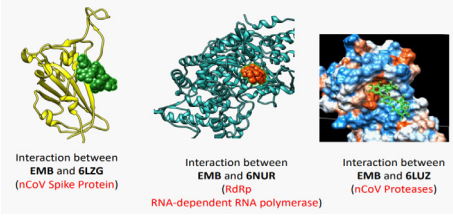




No.	Protein	Protein Name	Compound	Binding Energy	
1	6LZG	Spike Protein	EMA	-8 kcal/mol	★
2	6NUR	RdRP	EMA	-9.5 kcal/mol	★
3	6LU7	Proteases	EMA	-9.2 kcal/mol	★

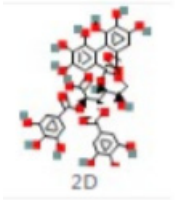
Emblicanin-B

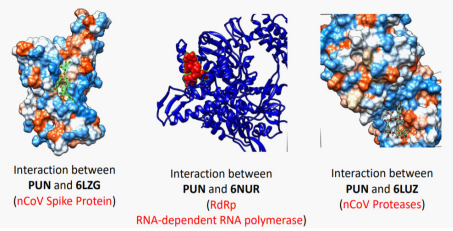




No.	Protein	Protein Name	Compound	Binding Energy	
1	6LZG	Spike Protein	EMB	-7.8 kcal/mol	★
2	6NUR	RdRP	EMB	-9.4 kcal/mol	★
3	6LU7	Proteases	EMB	-8.5 kcal/mol	★

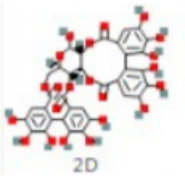
Punigluconin

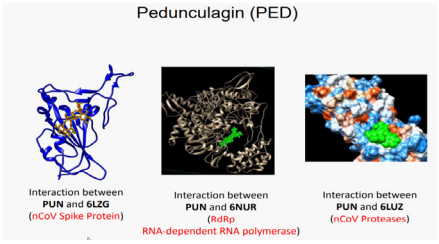




No.	Protein	Protein Name	Compound	Binding Energy	
1	6LZG	Spike Protein	PUN	-8.0 kcal/mol	★
2	6NUR	RdRP	PUN	-9.3 kcal/mol	★
3	6LU7	Proteases	PUN	-7.7 kcal/mol	★

Pedunculagin(PED)





No.	Protein	Protein Name	Compound	Binding Energy	
1	6LZG	Spike Protein	PED	-8.6 kcal/mol	★
2	6NUR	RdRP	PED	-8.7 kcal/mol	★
3	6LU7	Proteases	PED	-9.1 kcal/mol	★

The protein PDB ID 6NUR (nCoV RdRP has a comparatively higher binding affinity to many of the active compounds than the other two proteins. Binding of EMA-Emblicanin A from VNelli was highest compared to others

Pedunculagin from Nelli showed the highest binding affinity to spike protein, and Emblicanin A and B from Nelli showed the highest binding affinity to PDB ID-6LUZ that is nCoV Proteases.

Based on the analysis of bio active compounds from Nelli had shown the highest binding affility with all these three proteins(6NUR,6LZG and 6LU7).Hence this bio active co mpound alone can be consider for treatment or in combination with majal can also have synergistic effect on Corona virus.

Comparison of binding energy of different bioactive compounds of swastha kada

No	Protein	Protein name	PIN	PIT	CU3	ROS	API	EMA	EMB	PUN	PED
1	6LZG	Spike protein	*-7.5*	*-7.4*	*-7.2*	*-7.5*	*-7.2*	**-8.0**	**-7.8**	**-8.0**	**-8.6**
2	6NUR	EdRp	*-7.8*	**-8.2**	*-7.0*	*-7.4*	**-8.0**	**-9.5**	**-9.4**	**-9.3**	**-8.7**
3	6LU7	Proteases	*-7.0*	-6.8	*-7.0*	*-7.2*	-6.8	**-9.2**	**-8.5**	*-7.7*	**-9.1**

***Italics**:* Shows Maximum binding energy.
Bold: Shows highest binding energy.

Discussion

In this study, molecular docking was done against three different proteins of the nCoV with five ingredients of the swatha kada kashayam. Among the five, bioactive compounds of Nelli (Emblicanin-A and B, Punigluconin, Pedunculagin(PED) is having higher antiviral effect against all three proteins of nCoV and Curcumin II acid bio active compound of manjal, Rosmarinic acid present in Tulsi . Piperitin (PIN and PIT) is also having higher antivriral effect against three major proteins of nCoV. Dozens of proteins are coded by coronavirus, some of which are involved in viral replication and entry into cells. Main protease (Mpro/3CLpro) is a key enzyme for coronavirus replication [7], and surface Spike (S) glycoprotein (S protein) is an important binding protein for fusion of the virus and cellular membrane via cellular receptor Angiotensin-Converting Enzyme 2 (ACE2) (8). SARS-Cov-2 is easily transmitted because the S protein on the surface of the virus binds very efficiently to ACE2 on the surfaces of human cells [8]. Therefore, Mpro/3CLpro and S protein are ideal targets for drug design and development. Efforts have been made globally to obtain vaccines or drugs for the prevention or treatment of COVID-19 infections. So far, remdesivir is the most promising COVID-19 drug, although the FDA has approved the use of chloroquine and hydroxychloroquine. As study based on molecular dynamics stimulation of a docked protein ligand compound, nelfinavir was predicted to be COVID-19 drug candidates as the best potential inhibitor against main protease [9]. On the other hand despite little evidence on the effectively of chloroquine and hydroxyl chloroquine these two antimalarial agents has approved by food and drug administration for emergency coronavirus treatment [10]. Because COVID-19 is a new disease with serious global health problems, research is still needed including finding specific therapeutic regiments to overcome the morbidity and mortality it causes. Natural spices and plants are one of the medicinal active compound sources that have been widely used to treat disease caused by microbes [11,12]. There are many plant bioactive compounds reported to have activities as antifungal, antibacterial and antiviral. The

natural product that have been reported to have antiviral activity can be used as a starting point in finding potential bioactive compound candidates against SARS-CoV-2. Molecular docking can be used to predict how receptor protein interact with bioactive compounds [13]. Several previous studies have been performed to investigate bioactive compounds in plants that have the potential to inhibit the proliferation of viruses [14,15]. Understanding the importance of early screening for the potential of bioactive compounds to find drug candidates or prevention of viral infections, this study aimed to evaluate various bioactive compounds of swastha kada kashayam known by the community against three different proteins of nCoV19 by a molecular docking approach. The findings of the research showed higher effect against n CoV, but the further research is needed to show the specific regiments to overcome COVID-19.

Conclusion

At times of adversity, such as what the world is passing through today due to the COVID-19 virus pandemic, there is an urgent need to develop a rapid yet reliable strategy to counter the disease. One such

approach that we have employed and presented here is to explore the repositioning or repurposing of some of the most common natural products that are used in our day to day life, especially Indian. We used spices and vegetables and explored if they bind to the active sites of COVID-19 proteases, 6LU7 and 6Y2E, critical for viral replication. Our findings shows that several of the natural bio-active compounds that are commonly used by Indian had better binding free energy with three main proteins of SARS-CoV-2. These compounds have a potential as anti-viral phytochemicals that may inhibit the replication of virus. Bioactive compounds present in Nelli, Tulsi and pepper had more antiviral effects against SARS-CoV-2, but further in vitro and clinical trials are needed to evaluate these potential inhibitors as clinical drugs. The results revealed here are preliminary and the optimism needs to be tempered with more detailed dynamic simulation studies for getting a better insight into the mode of inhibition. However as mentioned elsewhere, the purpose of this article is to draw urgent attention to the promise of some of these compounds, and galvanize attention of the Indian scientific community to these possibilities and hopefully lead to the development of some drugs against COVID-19 virus in the near future.

Acknowledgement

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