Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Research Article (Experimental)

An ayurvedic perspective along with in silico study of the drugs for the management of SARS-CoV-2

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ABSTRACT

Background: COVID-19 is the disease caused by SARS-CoV2, it was identified in Wuhan, China, in 2019. It then extended across the globe and was termed as a pandemic in 2020. Though research work on its vaccine and drugs are carried out across the globe, it is even necessary to look over it through alternative sciences.
Objective: The objective of this study is to look over the disease through Ayurvedic perspective, analyse possible pathologies, select appropriate drugs and to study in-silico screening on these selected drugs.
Materials & Methods: Available symptoms of COVID-19 were thoroughly studied and reviewed through Ayurveda classics, internet, preprints, etc. to understand the nature of the disease with the Ayurvedic perspective. The molecular Docking and Grid were generated through Pyrx Software with Autodock. The Lipinski Rule of Five data generated from Swiss ADME software and Target prediction of selected phytoconstituents were done by Swiss target prediction.
Results: In Ayurveda, COVID-19 can be considered as *Janapadaudhwans*, *Vata-Kaphaja Sannipatika Jwara, Aupasargika Vyadhi,* and *Dhatupaka Awastha*. In the molecular docking study, the binding energy and inhibition of 6 Gingesulphonic acid from Zingiber officinalis *(Sunthi)* is greater than hydroxychloroquine and quinine. Most of the selected phytoconstituents follow the Lipinski rule of five. Target prediction of selected phytoconstituents was done on target of SARS-CoV-2, humoral immunity, and antiviral activity. Every selected phytoconstituents works on minimum one of the targets.
Conclusion: Thus, from the above results obtained from reviewing Ayurveda classics and after the virtual screening of selected drugs we can conclude that *Nagaradi Kashaya (Sunthi, Puskarmoola, Kantakari, Guduchi)* may have appreciable results in combating SARS-CoV-2. Thus, *Nagaradi Kashayam*, a classical formulation can be a trial candidate for conducting further clinical trial.

1. Introduction

The outbreak of COVID-19, caused by the Noval Corona Virus (nCoV) that is now officially designated as Severe Acute Respiratory Syndrome-Related Coronavirus SARS-CoV-2, represents a pandemic threat to global public health. Although the epicentre of the COVID-19 outbreak in December of 2019 was located in Wuhan China, this disease has spread to more than 213 countries with over 1,00,00, 000confirmed cases and still continuing.

Ayurveda is a life science having a holistic approach in dealing with different types of diseases. It has a completely different way of looking at any new diseases. Understanding of any disease in Ayurveda is done by five elements, i.e. *Hetu, Purvarupa, Rupa, Upashaya-Anupashaya, Samprapti* [1]. By these elements, a physician gets to know about the nature of the diseases *(Vikara Prakruti)*, site of the diseases *(Adhisthanam)*, the course of the disease *(Samprapti)* and about the aggravating factors of the disease. By understanding these factors in detail, a physician can design the preventive measures and treatment protocol for the disease. Though Ayurveda focuses on the concept of individualism and accepts that each individual is unique but in this situation of the pandemic when many people are affected by the same set of

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symptoms, one can briefly design a treatment policy by considering the available information about the disease.

Thus, it is the need of an hour to think out of the box so here is an initiation to think about the present pandemic COVID-19 through Ayurveda perspective. The main objective of this study is to look over the disease through Ayurvedic perspective, analyse possible pathologies, select appropriate drugs and to study in-silico screening on these selected drugs. Though, there are many protease of the disease present but this study is limited to virtual screening against main protease (Mpro) of the virus. The present piece of work studies the virtual screening of the phytoconstituents which can help for a further *invitro, invivo* research for COVID-19.

According to WHO, people who have co-morbidities and those over 60 years of age have a higher risk of developing severe symptoms of COVID-19 [2]. Common symptoms of COVID-19 include fever *(Jwara),* tiredness *(Shrama, Klama) and* dry cough*(-Shushka Kasa).* Other symptoms include shortness of breath *(Shwasa),* aches and pains *(Anga Mardana*), sore throat *(Kantha Shoola),* very few people will report diarrhoea (*Drava Mala)*, nausea *(Hrullasa)* or a running nose *(Peenasa).*

1.1. Possible ayurvedic concepts

With the help of the available data regarding COVID-19 and after going through the Ayurveda classics thoroughly, the following possible pathological models can be drawn.

1.1.1. Janapada-Udhwamsa Vikara

COVID-19 has evolved itself into a pandemic, affecting a large population irrespective of their physical features, dietary patterns, psychological attributes, etc., Ayurveda considers it as a *Janapada-Udhwamsa Vikara* [3].

1.1.2. Vata Kaphaja Jwara

By looking at its symptomatology, it resembles with the classical features of *Vata Kaphaja Jwaram* mentioned in the classics [4].

1.1.3. Bhutabhishangaja Jwara

It can also be grouped under the class of *Aagantuja Vikara* with special reference to the class of *Bhutabhishangaja Jwara.* The management of *Aagantuja Vikara* should follow the lines of *Nija Vikara* [5].

1.1.4. Aupasargika Jwara

COVID-19 is transmitting from one human to others by direct contact *(Gatra Sansparshat)*, air droplet *(Ni-shwasat)*. This type of the disease is termed as *Aupasargika* in Ayurveda [6].

1.1.5. Dhatu Paka Awastha

Few severe conditions show symptoms of *Sannipata Jwara* leading to *Dhatupaka Awsatha,* where all three *Doshas* get vitiated and suppress the *Dhatu Bala* (immunity) of an individual leading to *Oja-Kshaya* and ultimately death [7].

1.2. Etiology of disease in ayurveda terms

Dosha — Vata, Kapha Pradhana
Dushya- Rasa, Rakta, Mansa, Oja
Adhisthana- Koshtha (Aamashaya **and** *Ura Pradesha)*
Strotasa- Pranavaha Strotasa, Annavaha Strotasa
Awastha- **Stage 1***: Vata Kaphaja Jwara*
Stage 2*: Vata Kaphaja Sannipatika Jwara*
Stage 3*: Sannipatika Jwara, Dhatupaka Awastha.*
Upashaya- Pravara Bala- Uttama Upashaya
Anupashaya: Vrudha Vaya — Anupashaya.

2. Material and methods

2.1. Proteins/macromolecules

COVID-19 3clpro/Mpro (PDB ID: 6LU7) structures was obtained from PDB in.pdb format. PDB is an archive for the crystal structures of biological macromolecules, worldwide. The 6LU7 protein contains two chains, A and B, which form a homodimer. Chain A was used for macromolecule preparation [8]. The coronavirus main protease (Mpro), which plays a pivotal role in viral gene expression and replication through the proteolytic processing of replicase polyproteins, is an attractive target for anti CoV drug design [9].

2.2. Ligand and drug scan

The 160 3-dimensional (3D) structures were obtained from PubChem in.sdf format. PubChem is a chemical substance and biological activities repository consisting of three databases, including substance, compound, and bioassay databases. The compounds used in the present study is shown in Table 2, along with its binding energy with protein [10].

Table 1
Ayurvedic properties of certain potential drugs [18].

Drug name	Latin name	Family	Rasa	Guna	Virya	Doshaghnata	Karma
Sunthi	*Zingiber officinale* Roscoe	Zingiberaceae	*Katu*	*Snigdha, Teekshna*	*Ushna*	*Vatakapha* hara	*Deepana, Rochana, Shoolaprashamana*
Pushkarmoola	*Inula racemose* Hook.F.	*Asteraceae*	*Katu Tikta*	*Laghu*	*Ushna*	*Vatakapha hara*	*Shwasahara, Parshwashool Nut, Jwarghna, Shwaas*
Guduchi	*Tinospra cordifolia* Miers	*Menispermaceae*	*Tikta, Katu*	*Laghu, Snighdha,*	*Ushna*	*Tridoshahara,*	*Jwaraghna, Rasayana, Kasa, Pandu.*
Kantakari	*Solanum zanthocarpum* L.	*Solanaceae*	*Katu Tikta*	*Deepana, Laghu, Sara, Ruksha,*	*Ushna*	*Kapha-vataghna*	*Shwasa —Kasa Jit, Pachani, Parshwaroga*
Pippali	*Piper longum* L.	*Piperaceae*	*Katu*	*Deepana, Snighdha, Laghu*	*Anushna*	*Vata-Shleshmahara*	*Vrushya, Rasayana, Shwasa-Kasa Hara*
Haridra	*Curcuma longa* L.	*Zingibraceae*	*Katu, Tikta*	*Ruksha*	*Ushna*	*Kapha-Pitta hara*	*Prameha-Hara, Kushthaghna*
Shatavari	*Asparagys racemosus* Willd.	*Liliaceae*	*Tikta, Madhura*	*Snighdha, Guru*	*Sheeta*	*Vata-Pittaghna*	*Rasayani, Balya,*
Gokshura	*Tribulus terrestris* L.	Zygophyllaceae	*Madhura*	*Snighdha, Guru*	*Sheeta*	*Vatahara*	*Balya, Basti-Shodhana, Vrushya, Shwaas-Kaas-Ghna*
Yashtimadhu	*Glycyrrhiza glabra* L.	*Fabaceae*	*Madhu*	*Snighdha, Guru*	*Sheeta*	*Pitta-Vata-Ghna.*	*Balya, Shukral*
Musta	*Cyperus rotundus* L.	*Cyperaceae*	*Katu, Tikta, Kashaya*	*Laghu, Ruksha.*	*Sheeta*	*Kapha-Pitta Hara*	*Deepana- Pachana, Grahi, Jwaraghna*

Table 2
Properties of COVID-19 M^{pro} potential inhibitor candidates.

Chemical constituent	Binding energy	Inhibition	Lipinski rule		Target Prediction
Hydroxychloroquine	−3.85 kcal/mol	1.50 mM	Molecular weight	335.87	Tyrosine-protein kinase SYK
			#H-bond acceptors	3	Tyrosine-protein kinase LCK
			#H-bond donors	2	Macrophage colony stimulating factor receptor
			iLOGP	3.58	
			Lipinski #violations	0	
Quinine	−5.62 kcal/mol	0.0761 mM	Molecular weight	324.42	Tyrosine-protein kinase ABL
			#H-bond acceptors	4	Tyrosine-protein kinase LCK
			#H-bond donors	1	Tyrosine-protein kinase SYK
			iLOGP	3.36	Macrophage stimulating protein receptor
			Lipinski #violations	0	
***Sunthi* (*Zingiber officinale* Roscoe)**					
6gingesulphonic acid	−6.20 kcal/mol	5.36 mM	Molecular weight	358.45	Interferon-induced, double-stranded RNA-activated protein kinase
			#H-bond acceptors	6	Angiotensin converting enzyme
			#H-bond donors	2	Tyrosine-protein kinase LCK-
			iLOGP	2.48	Tyrosine-protein kinase HCK
			Lipinski #violations	0	
***Pushkarmool* (*Inula racemose* Hook.F.)**					
Alantolactum	−6.70 kcal/mol	0.01540 mM	Molecular weight	232.32	Inhibitor of nuclear factor kappa B kinase beta subunit
			#H-bond acceptors	2	T-cell protein-tyrosine phosphatase p
			#H-bond donors	0	Protein-tyrosine phosphatase 1B
			iLOGP	2.75	
			Lipinski #violations	0	
***Guduchi* (*Tinospora cordifolia* Miers)**					
Berberine	−7.00 kcal/mol	0.01757 mM	Molecular weight	336.36	Inhibitor of nuclear factor kappa B kinase beta subunit
			#H-bond acceptors	0	
			#H-bond donors	0	
			iLOGP	0	
			Lipinski #violations	0	
***Kantakari* (*Solanum xanthocarpum* L.)**					
Stigmasterol	−6.90 kcal/mol	0.01083 mM	Molecular weight	412.69	Angiotensin converting enzyme
			#H-bond acceptors	1	Indoleamine 2,3dioxygenase
			#H-bond donors	1	Protein-tyrosine phosphatase 1B
			iLOGP	4.76	
			Lipinski #violations	1	
***Pippali* (*Piper longum* L.)**					
Bisdemethoxycurcumin	−6.90 kcal/mol	0.10335 mM	Molecular weight	308.33	Glycogen synthase kinase-3 beta
			#H-bond acceptors	4	Inhibitor of NFkappa-B kinase (IKK)
			#H-bond donors	2	Macrophage colony stimulating factor receptor
			iLOGP	1.75	
			Lipinski #violations	0	
***Haridra* (*Curcuma longa* L.)**					
Demethoxycurcumin	−6.20 kcal/mol	0.188.74 mM	Molecular weight	338.35	Inhibitor of NFkappa-B kinase (IKK)
			#H-bond acceptors	5	Toll-like receptor (TLR7/TLR9)
			#H-bond donors	2	Tyrosine-protein kinase Lyn
			iLOGP	2.78	Tyrosine-protein kinase BTK
			Lipinski #violations	0	
***Shatavari (Asparagus racemosus* Willd)**					
Kaempferol	−6.70 kcal/mol	0.06181 mM	Molecular weight	286.24	Tyrosine-protein kinase SRC
			#H-bond acceptors	6	Tyrosine-protein kinase receptor UFO
			#H-bond donors	4	Interleukin-8 receptor A
			iLOGP	1.7	
			Lipinski #violations	0	
***Gokshura* (*Tribulus terrestris* L.)**					
Gitogenin	−8.00 kcal/mol	0.00366 mM	Molecular weight	432.64	Tyrosine-protein kinase JAK3
			#H-bond acceptors	4	Nuclear receptor ROR-gamma
			#H-bond donors	2	
			iLOGP	4.19	
			Lipinski #violations	1	
***Yashtimadhu* (*Glycyrriza* g*labra* L.)**					
Glycerol	−8.47 kcal/mol	0.00062273 mM	Molecular weight	92.09	Glycogen synthase kinase-3 beta
			#H-bond acceptors	3	Tyrosine-protein kinase ABL
			#H-bond donors	3	Tyrosine-protein kinase JAK1
			iLOGP	0.45	Tyrosine-protein kinase JAK3
			Lipinski #violations	0	Tyrosine-protein kinase LCK
***Musta* (*Cyprus* r*otundus* L.)**					
Patcholane	−6.12 kcal/mol	0.03258 mM	Molecular weight	206.37	Interleukin-6 receptor subunit beta
			#H-bond acceptors	0	Tyrosine-protein kinase JAK1
			#H-bond donors	0	Tyrosine-protein kinase JAK2
			iLOGP	3.22	Tyrosine-protein kinase JAK3
			Lipinski #violations	1	Tyrosine-protein kinase TYK2

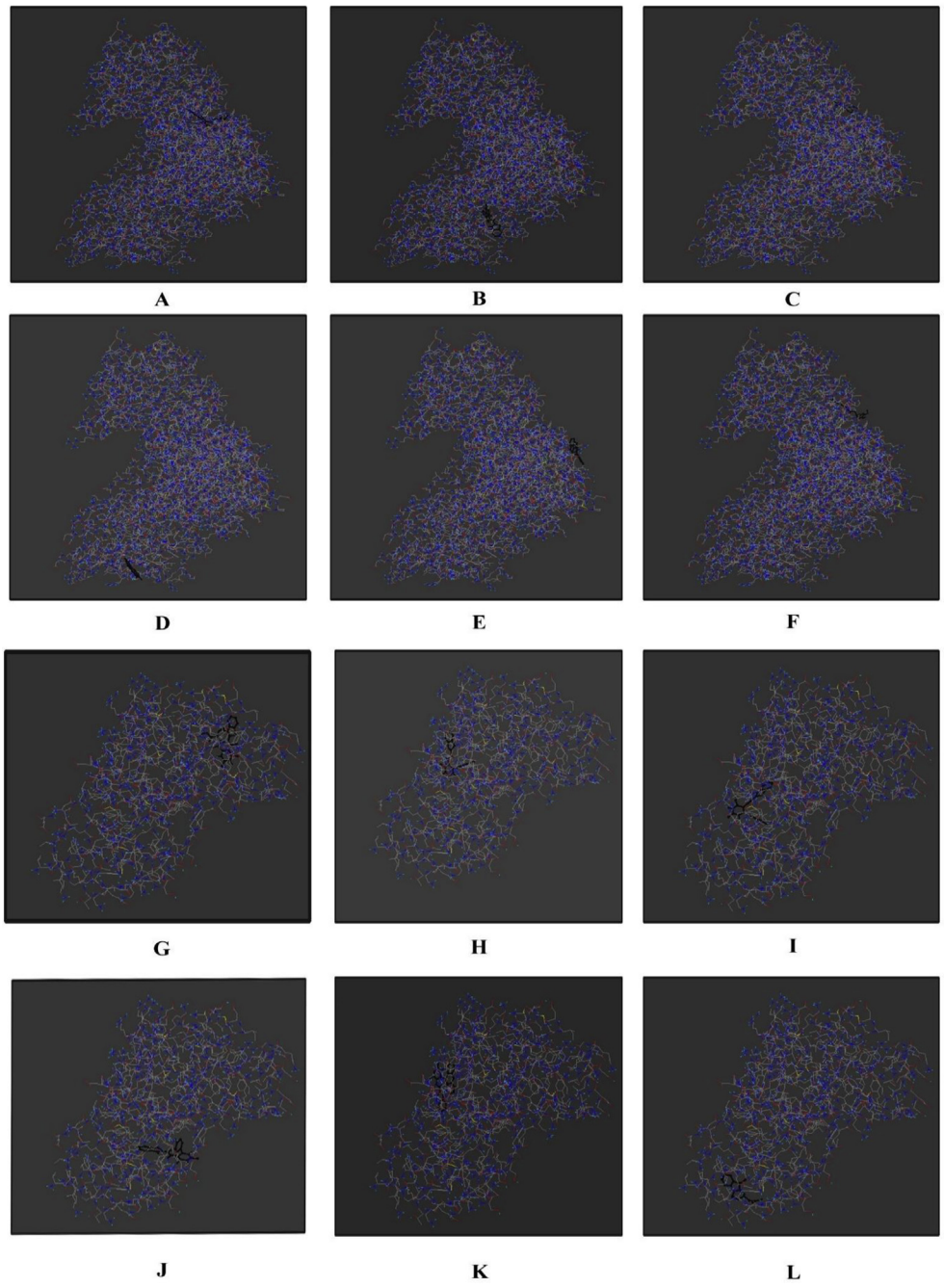

Fig. 1. Visualisation of selected phytoconstituents through pyrx. A represents visualisation of hydroxychloroquine with protein 6lu7. B represents visualisation of quinine with protein 6lu7. C represents visualisation of *Sunthi* (*Zingiber officinale* Roscoe) with protein 6lu7. D represents visualisation of *Pushkarmool* (*Inula racemose* Hook.F.) with protein 6lu7. E represents visualisation of *Guduchi* (*Tinospora cordifolia* Miers) with protein 6lu7. F represents visualisation of *Kantakari* (*Solanum xanthocarpum* L.) with protein 6lu7. G represents visualisation of *Pippali* (*Piper longum* L.) with protein 6lu7. H represents visualisation of *Haridra* (*Curcuma longa* L.) with protein 6lu7. I represents visualisation of *Shatavari (Asparagus racemosus* Willd) with protein 6lu7. J represents visualisation of *Gokshura* (*Tribulus terrestris* L.) with protein 6lu7. K represents visualisation of *Yashtimadhu* (*Glycyrriza glabra* L.) with protein 6lu7. L represents visualisation of *Musta* (*Cyprus rotundus* L.) with protein 6lu7.

2.3. Molecular docking

The Ligand was docked against the protein and the interactions were analyzed by using Pyrx 0.8. For the docking of ligands into protein active site and to estimate the binding affinities of docked compounds and for generation of grid, studies were carried out using pyrx AutoDock wizard with MGL tools 1.5.6 installed in a Pentium ®Dual −Core CPU T4200 machine running on a 2.0 GHz Intel Core processor with 2 GB RAM by using Lamarkian Algorithm. The scoring function gives score based on best docked ligand complex is picked out [11].

2.4. Swiss ADME

Drug-like properties were calculated using Lipinski's rule of five, which proposes that molecules with poor permeation and oral absorption have molecular weights >500, C logP >5, more than 5 hydrogen-bond donors, and more than 10 acceptor groups.

Adherence with Lipinski's rule of five were calculated using SWISS ADME prediction [12–14].

2.5. Swiss target prediction

The active site of a protein was determined using the Swiss Target Prediction. The unique engine behind swiss target prediction, extensively detailed elsewhere, calculate the similarity between the users query compound and those compiled in curated, cleansed collection of known actives in well defined experimental binding assays. The quantification of similarity is 2 folds. It gives the active site bind to the molecule [15,16].

3. Results and Discussion

Within weeks from when the genetic sequence of the SARS-CoV-2 was made available, structural biologists have used these techniques to see proteins that make up the SARS-CoV-2 virus. In this study, as shown in Table 1, we have selected 10 drugs on the basis of their ayurvedic properties which can probably be used for SARS-CoV-2. For every plant we carried out molecular docking on each phytoconstituent present in the plant. From this, we selected one phytoconstituent from every plant which is having higher binding energy and inhibition to protein molecule of SARS-CoV-2. The protein molecule used for the study is 6lu7. At present, the hydroxychloroquine and quinine are being used for the treatment of COVID-19 [17]. Thus, we are comparing the efficacy of the following drugs with the hydroxychloroquine and quinine. The molecular docking, Lipinski Rule of Five and Target prediction were calculated. Target prediction for SARS-CoV-2, Humoral immunity and antiviral activity were taken and searched on the selected phytoconstituents. The data is shown in Table 2. Grid of the phytoconcstituents is shown in Fig. 1.

From studying the patho-physiology of the disease through Ayurveda perspective, we have selected 10 Ayurvedic drugs based upon their properties. The molecular docking study gives encouraging results for the selected phytoconstituents. 6 gingesulphonic acid which is present in *Sunthi* is having higher binding energy and inhibition constant than hydroxychloroquine and quinine whereas other phytoconstituents having less binding energy and inhibition constant than 6 gingesulphonic acid. Most of the selected compound follows Lipinski Rule of Five so they are pharmacologically active compounds. Also target prediction of selected phytoconstituents were carried out in which we got the target which are effectable on SARS-CoV-2, Humoral immunity and Antiviral activity.

From overviewing the Ayurvedic perspective, etiology of the disease and studying the phytoconstituents of the drugs, we hypothesized to use *Nagaradi Kashaya* which includes ***Sunthi*** (*Zingiber officinale* Roscoe), ***Pushkarmool*** (*Inula racemose* Hook.F.), ***Guduchi*** (*Tinospora cordifolia* Miers.), ***Kantakari*** (*Solanum virginianum* L.) for combating COVID-19. The above combination is mentioned in *Jwara Chikitsa.* As most of the drugs are having *Tikta Rasa, Laghu-Guna* and *Pachana Karma.* It helps in *Aama Pachana.* It also has *Kasa-Shwasa-ghna* properties and are indicated for *Jwara, Kasa, Shwasa* and *Parshawashoola* i.e. the symptoms similar to SARS-CoV-2. Primary evidence for the usage of these drugs, virtual screening of the drugs shows positive results.

As though we use phytoconstituents for this study but further research is necessary to investigate the potential uses of the medicinal plants as a whole.

4. Limitations of the study

Although computer-aided drug design and network pharmacology have been widely used and developed, there still have deficiencies and limitations: (1) The model maturity and computational accuracy of computer docking algorithms need to be further improved. (2) Due to the structure-based methodology, several compounds are not suitable for computer-aided design because of their special structure characteristics. (3) A large number of databases can improve different information for the obtained potential targets, the progress of the selection of these databases and their effective information annotation, still requires continuously practical activities to optimize. With the advancement of computer science, and the constant optimization of algorithms, including the maturity of the protein model. Through more practical researches and development examples are available to upgrade the entire process of in silico methodology, we believe that in the future, this methodological process will enable the discovery of new drugs more efficiently, accurately and quickly. This methodology will be more widely useable in future work on revealing and predicting the basis of medicinal materials.

5. Conclusion

Currently, COVID-19 has emerged in the human population and is a potential threat to global health worldwide. Many drug research and developments projects as well as vaccine development research work is in progress. The aim of this study is to examine several medicinal plant-derived compounds that may be used to inhibit the COVID-19 infection pathway.

Thus, from the above results obtained from reviewing Ayurveda classics and after the virtual screening of selected drugs we can conclude that *Nagaradi Kashaya* may have appreciable results in combating SARS-CoV-2. *Nagaradi Kashaya* can be a trial candidate for conducting further clinical trial.

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None declared.

Conflicts of interest

None.

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