Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 12 [7] June 2023: 227-234

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Repurposing of Isolated Phytochemicals for Its Antiviral Activity Against SARS Covid-19 Through *In-Silico* Evaluation

Agasa Ramu Mahesh[1*], Josephine Jenita Leno[2], Veda B Hacholli[3]
[1*] Faculty of Pharmacy, MS Ramaiah University of Applied Sciences. Bengaluru, Karnataka, India.
[2] College of Pharmaceutical Sciences, Dayananda Sagar University, Bengaluru, Karnataka, India.
[3] Nitte College of Pharmaceutical Sciences, Bangalore, Karnataka, India.
Corresponding author: armahesh@hotmail.com

ABSTRACT

COVID-19 is a deadly disease, where the infection is caused by SARS-CoV-2. Since no specific medication is available to treat COVID-19, designing of new drug is important and essential. In this regard, In-silico method plays an important role, as it is rapid and cost effective compared to the trial-and-error methods using experimental studies. Natural products were safe and easily available to treat coronavirus affected patients, in the present alarming situation. In this paper 98 phytochemicals, which were reported to be antiviral, have been selected as small molecules in molecular docking study of spike protein of SARS-CoV2 with different protein molecules such as 6LU7, 4MM3, 2GHV, 6M71 and 6M17. All the phytochemicals were also subjected to In-silico ADME/T studies out of which more than 24 compounds were found as potent as and few compounds such as Rhein more potent than the currently used synthetic antiviral drug viz., remdesivir. The binding affinities of phytochemical Rhein found to be better than that of remdesivir, viz., for 6LU7 the binding affinity of remdesivir was -7.9 and Rhein was -15.1, for 4MM3 the binding affinity of remdesivir was -7.2 and Rhein was -9.8, for 2GHV the binding affinity of remdesivir was -7.2 and Rhein was -12.4, for 6M71 the binding affinity of remdesivir was -8.1 and Rhein was -14.9, and for 6M17 the binding affinity of remdesivir was -7.7 and Rhein was -15.1. In the results of the molecular properties of the phytochemicals used in this study. The ADME/T. The predicted toxicological profile of all the tested phytochemicals and has no mutagenic potentials against bacteria (AMES toxicity) but vernodalol and vernodalin could be toxic to bacteria. None of the phytochemicals has adverse effects on the hepatic or dermal cells. The phytochemicals were not inhibitors of human ether-a-go-go-related gene (hERG) hERG I and hERG II except veronicoside A which may inhibit hERG II. All the phytochemicals have relatively low maximum recommended tolerated dose values.

Keywords: *COVID-19, SARS-CoV-2, 6LU7, 4MM3, 2GHV, 6M71, 6M17, ADME/T, In-silico.*

Received 09.05.2023 Revised 19.05.2023 Accepted 30.06.2023

INTRODUCTION

The COVID-19 pandemic has resulted in an increase of morbidity and mortality rates. The plan of action here was to look for In-silico potential of phytoconstituents against SARS COV-2 by computer aided protocols against the viral proteins.

Plants and their constituents have been immensely important for human welfare since ancient times [1, 2, 3]. Several antiviral compounds from plant constituents were being used in many studies. Researchers around the world were screening secondary metabolites of anti- viral plants for their therapeutic activities and were trying to find novel compounds [4, 5]. It has been well established that In-silico studies were very useful in drug discovery. This technique conserves information in terms of money and time [6, 7, 8]. Hence, we have reviewed and screened a library of selected plant phytoconstituents against the viral protein of SARS COV-2.

Pimpinella anisum L. is a plant of Umbelliferae family and is one of the oldest medicinal plants. Anise seeds have been used in Iranian traditional medicine for its various pharmacological actions. Various different studies have showed the plant properties such as antimicrobial, antifungal, antiviral, antioxidant, muscle relaxant, analgesic, anticonvulsant, hypoglycaemic and hypolipidemic activity as well as different effects on gastrointestinal system have been reported [7]. It has also been reported for antiviral activity against influenza (A/WS/33) and exhibited strong anti-influenza A/WS/33 virus activity [7, 9].

The major constituents of anise were reported as trans-anethole, estragole, linalool, limonene, chavicol, alpha-pinene, anisaldehyde, coumarins, umbelliferone, estrols, terpene hydrocarbons [6, 9, 10]. Few

selected constituents show anti-inflammatory, anticancer, anti- hyperlipidemic, antimicrobial, antinoceptive, analgesic, anxiolytic, antioxidant, antiviral, neuroprotective and various other properties [4, 11].

Clary sage (Salvia sclarea L.) is cultivated worldwide and is known for its high value essential oil. The oil possesses high biological and therapeutic activity. It has reported analgesic, anti-inflammatory, antimicrobial, antidiabetic, anti-hypertension, cytotoxic effects. The major constituents of Clary sage were Linalayl acetate, Linalool, α–Terpineol, Geranyl acetate, Cinnamaldehyde and β–myrcene [4]

Linalool and terpineol were monoterpene alcohols present as major constituents of different plant essential oil. A study has also reported highly effective antiviral activity of α– Terpineol against avian influenza (H5N1) virus [4]. Linalyl acetate has also shown high antiviral activity against H5N1, and A/WS/33 virus as reported in studies [4, 10, 12].

Eucalyptus essential oil has conventionally been used to treat respiratory tract disorders and infections. Pharyngitis, bronchitis, and sinusitis have also been treated by inhalation of Eucalyptus derivatives. Antiviral activity of Eucalyptus essential oils against Adenovirus, mumps and herpes simplex viruses have been reported in various studies [6]. A study reported that eucalyptus oil aerosols possess strong antiviral action and are capable of inactivating model viruses (Influenza A virus and E. coli phage M13) with efficiency of more than 95 % [9].

1,8-cineole is the major compound of eucalyptus followed by γ-terpinene, α-pinene, α- terpineol and p-cymene. Studies report that 1,8-cineole potentiates the antiviral activity of IRF3 and anti-HSV-1 activity by direct inactivation of free virus particles [6, 11, 12, 13]. Ocimum sanctum, also known as tulsi, is one of the most widely used ancient and traditional plants for its great therapeutic potential. Ocimum sanctum L. has also been reported to possess anticancer, antidiabetic, antifungal, antimicrobial, hepatoprotective, cardioprotective, antiemetic, antispasmodic, analgesic, adaptogenic and diaphoretic actions. The major compounds were ursolic acid, methyl eugenol, apegenin, gedunin and oleanolic acid. Ursolic acid posseses antitumor, hepatoprotective, anti-inflammatory (oral & topical), anti-ulcer, antimicrobial, anti-hyperlipidemic, and anti-viral activities [14]. The constituents of tulsi either in their pure form or as an extract can be effective inhibitors of SARS-CoV-2 and will be equally efficacious in preventing both viral attachment and replication [12, 15, 16, 17].

In this explicated we have explained the study we had carried out with the molecular docking and ADME/T studies of the various antiviral phytochemicals which could be used as an alternative to remdesivir which is widely used for treatment of COVID-19 currently.

MATERIAL AND METHODS

Selection of phytochemicals and proteins

The phytochemicals were selected based on various scholarly articles which were based on the antiviral phytochemicals, possessing antiviral activity, and considering that these phytochemicals may also inhibit the effect of SARS COV-2. The chemical structures for the phytochemicals were sketched using Chem draw 12.0, which were saved as SDF and clusters as MDL files. The crystal 3D structures of 5 different proteins of SARS COV 2 were selected and were retrieved from protein data bank, 3CL Pro-PDB ID: 6LU7, PLpro PDB ID: 4MM3, SGp -RBD PDB ID:2GHV, RdRp PDB ID:6M71 and ACE 2 PDB ID: 6M17.

Preparation of proteins

Thus obtained SARS COV-2 proteins namely 3CL Pro - PDB ID : 6LU7, PLpro PDB ID : 4MM3 , SGp -RBD PDB ID :2GHV , RdRp PDB ID:6M71 and ACE 2 PDB ID :6M17, from protein data bank (www.rcsb.org), were prepared using Swiss Pdb viewer, by checking for the missing amino acids. Hydrogen atoms and water molecules were removed, and charges were checked and were saved as prepared proteins. The binding site analysis was done using Castp3.0 and BIOVIA discovery studio client 2020.

Molecular Docking

Docking process was performed with five proteins and about ninety-eight phytochemical ligands, considering the standard drug as Remdesivir which Is been currently used as the choice of drug for COVID -19, The docking process was performed using PyRx Auto Dock Vina 0.8. In this process the prepared cluster and the finally prepared protein were taken to PyRx and these were converted to macromolecules and the grid adjustments were done according to site selection using Castp and BIOVIA Discovery studio 2020, the docking was performed and their binding energies were obtained and the binding energies of higher phytochemical ligands were taken for further In-silico ADMET Studies and drug likeliness studies were performed and their results were obtained. Form the resulted macromolecules interactions of amino acids binding sites and 2D and 3D were visualized using BIOVIA discovery studio.

ADME/T Studies

The solubility, pharmacodynamics, pharmacokinetics, and toxicological profiles of the listed phytochemicals and remdesivir were computed based on their ADMET (absorption, distribution, metabolism, elimination, and toxicity) studies using pkCSM tool (http://biosig.unimelb.edu.au/pkcsm/prediction) as described by Pires et al. [18]. The canonical SMILE molecular structures of the compounds used in the studies were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov).

RESULT

Total of 98 antiviral phytochemicals were screened using In-silico methods such as molecular docking, ADME/T studies, and drug likeliness studies out of which more than 24 compounds were found as potent as and few compounds such as Rhein more potent than the currently used synthetic antiviral drug viz., remdesivir. (Table 1-5)

Molecular docking studies were carried out on different proteins such as 6LU7: The crystal structure of COVID-19 main protease in complex, 4MM3: Crystal structure of SARS-CoV papain-like protease PLpro in complex with ubiquitin aldehyde, 2GHV: Crystal structure of SARS spike protein receptor binding domain, 6M71: SARS-Cov-2 RNA-dependent RNA polymerase in complex with cofactors and 6M17: The 2019-nCoV RBD/ACE-2- B0AT1 complex. In all the proteins, the binding affinities of phytochemical Rhein found to be better than that of remdesivir, viz., for 6LU7 the binding affinity of remdesivir was -7.9 and Rhein was -15.1 (Figure 1, 2), for 4MM3 the binding affinity of remdesivir was -7.2 and Rhein was -9.8 (Figure 3, 4), for 2GHV the binding affinity of remdesivir was -7.2 and Rhein was -12.4 (Figure 5, 6), for 6M71 the binding affinity of remdesivir was -8.1 and Rhein was -14.9 (Figure 7, 8), and for 6M17 the binding affinity of remdesivir was -7.7 and Rhein was -15.1 (Figure 9, 10).

Table 1 Molecular docking analysis of the tested compounds against COVID-19 protein 6LU7

Sl No.	Compound	Pub Chem CID	Binding energies (Kcal/mol)
1	Remdesiver	121304016	-7.9
2	Apigenin	5280443	-7
3	Ursolic Acid	64945	-7.3
4	Oleanolic Acid	10494	-7.5
5	Berberine	2353	-7.5
6	Tetrahydropalmatine	72301	-6.9
7	Tinosponone	15215479	-7.2
8	Xanosporic Acid	46879540	-7.9
9	Tinocordiside	177384	-7.3
10	Curcumin	969516	-7
11	Cyclocurcumin	77736151	-7.3
12	Silybin	31553	-8.1
13	Nictoflorin	5318767	-8.8
14	Astragalin	5282102	-7.5
15	Withanoside IV	71312551	-9.4
16	Racemoside A	102253062	-8.9
17	Glycyrrhizic Acid	14982	-8.7
18	Veronicoside	13848081	-8.5
19	Hydroxylamine-O-Decyl	34704	-7.8
20	Rhein	10168	-15.1
21	Ocotillone	12313665	-7.8
22	Ovatodiollide	6451060	-7.6
23	Nuciferine	10146	-7.2
24	Quercitin	5280343	-7.5
25	Hypericin	3663	-8.8

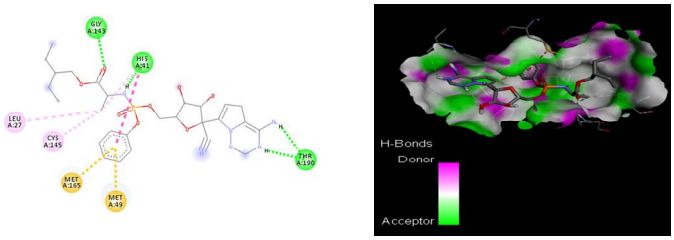

Figure 1. 2D & 3D Interactions of Remdesiver with the protein 6LU7.

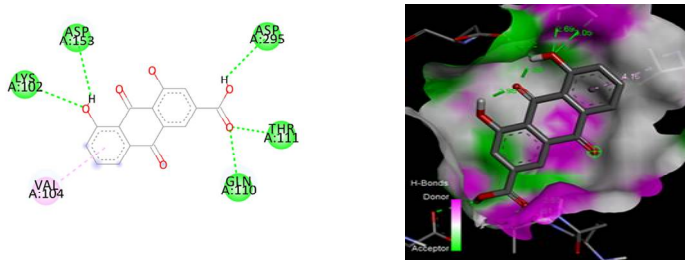

Figure 2. 2D & 3D Interactions of Rhein with the protein 6LU7.

Table 2 Molecular docking analysis of the tested compounds against COVID-19 protein 4MM3

Sl No.	Compound	Pub Chem CID	Binding energies (Kcal/mol)
1	Remdesivir	121304016	-7.2
2	Rhein	10168	-9.8
3	Phosphoric Acid	1004	-9.4
4	2,6,10 Trimethyl	101016390	-9.3
5	Phytol	5280435	-9.2
6	Veronicoside	13848081	-9.2
7	Excoecariatoxin	5281400	-8.9
8	Glycyrrhizin	3495	-8.8
9	β-Sitosterol	222284	-8.6
10	Ocotillone	12313665	-8.2
11	Diterpene	340129	-8.1
12	Apigenin-7-O-Glucoside	44257792	-8
13	Nictoflorin	5318767	-7.9
14	Kaempferol 3-O-Rutinoside	122173234	-7.9
15	All-Trans-Retinoic Acid	444795	-7.9
16	Phaseolin	91572	-7.9
17	Resveratrol	445154	-7.8
18	Glycyrrhizin	14982	-7.8
19	Tinocordiside	177384	-7.6
20	Silybin	31553	-7.6
21	Ovatodiollide	6451060	-7.6
22	Ursolic Acid	64945	-7.5
23	Scopadulcic Acid	11729855	-7.5
24	Cynaropicrin	119093	-7.4
25	Astragalin	5282102	-7.3

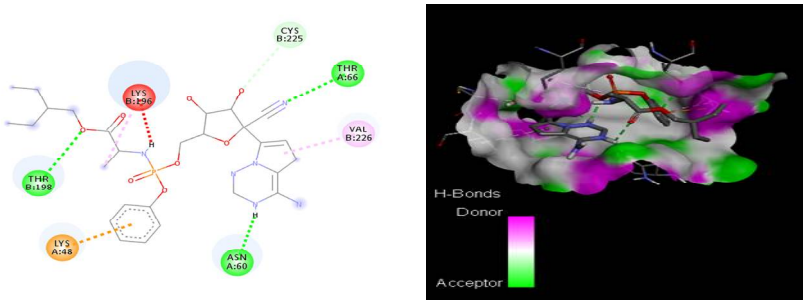

Figure 3. 2D & 3D Interactions of Remdesiver with the protein 4MM3.

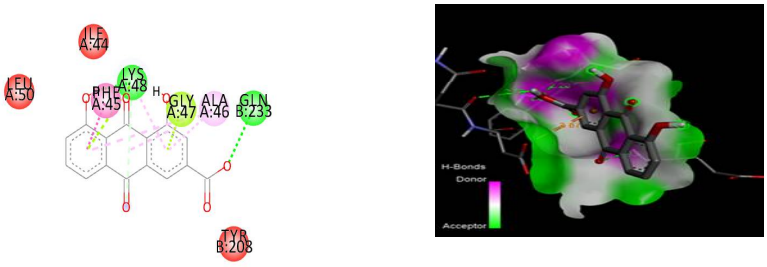

Figure 4. 2D & 3D Interactions of Rhein with the protein 4MM3.

Table 3 Molecular docking analysis of the tested compounds against COVID-19 protein 2GHV

Sl No.	Compound	PubChem CID	Binding energies (Kcal/mol)
1	Remdesivir	121304016	-7.2
2	Triptofordin C-2	13874096	-7.4
3	Ursolic acid	64945	-7.9
4	Oleanolic acid	10494	-7.8
5	Silybin	31553	-7.6
6	Nictoflorin	5318767	-7.8
7	Rhein	10168	-12.4
8	Glycyrrhizin	14982	-8.2
9	Phaseolin	91572	-8.3
10	β-Sitosterol	222284	-8
11	Cynaropicrin	119093	-7.6
12	Theaflavin digallate	5748168	-9.4
13	Diosmin	5281613	-8.1
14	18 β-glycyrrhetinic acid	10114	-7.9
15	Neohesperidin	232990	-7.8
16	Kaempferol 3-O-rutinoside	122173234	-7.7
17	Withanoside IV	71312551	-9.5
18	Phosphoric acid	1004	-9.4
19	Lycorine	72378	-9.4
20	Catechin	9064	-8.6
21	Ferulic acid	445858	-8.6
22	Ocotillone	12313665	-7.4
23	Camelliatannjin H	16132445	-7.3
24	Glycyrrhizin	4395	-8.3
25	Saikosaponins	167928	-7.8

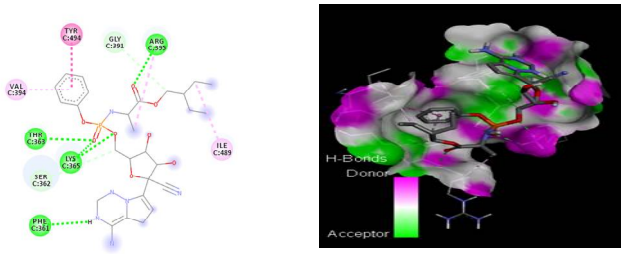

Figure 5. 2D & 3D Interactions of Remdesiver with the protein 2GHV.

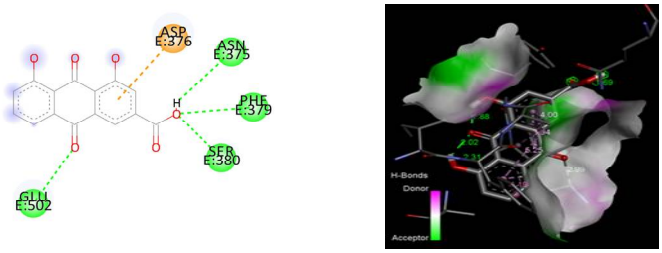

Figure 6. 2D & 3D Interactions of Rhein with the protein 2GHV.

Table 4 Molecular docking analysis of the tested compounds against COVID-19 protein 6M71

Sl No.	Compound	PubChem CID	Binding energies (Kcal/mol)
1	Remdesiver	121304016	-8.1
2	Rhein	10168	-14.9
3	Camelliatannin H	16132445	-10.8
4	Catechin	9064	-10.5
5	Theaflavin digallate	5748168	-10.1
6	Glycyrrhizin	3495	-10
7	Nictoflorin	5318767	-9.8
8	Kaempferol 3-O-rutinoside	122173234	-9.8
9	Gallic acid	370	-9.5
10	Rutin	-	-9.4
11	Saikosaponins	167928	-9.4
12	Hypericin	3663	-9.4
13	Kaempferol 3-O-robinobioside	-	-9.3
14	Ferulic acid	445858	-9.2

15	Chlorogenic acid	1794427	-9.1
16	Hesperidin		-8.9
17	Ursolic acid	64945	-8.3
18	Gedunin	3458	-8.3
19	Silybin	31553	-8.3
20	Mimusopic acid	6712545	-7.8
21	Triptofordin C-2	13874096	-7.7
22	Phytol	5280435	-7.7
23	Oleanolic acid	10494	-7.6
24	Tinosponone	15215479	-7.6
25	Apigenin	5280443	-7.5

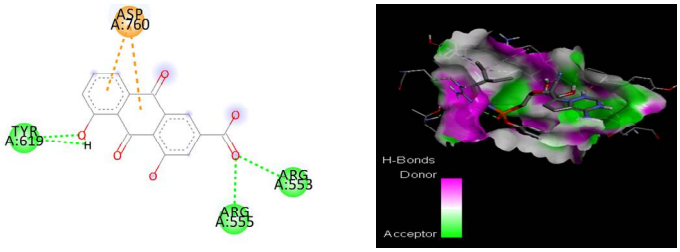

Figure 7. 2D & 3D Interactions of Remdesivir with the protein 6M71.

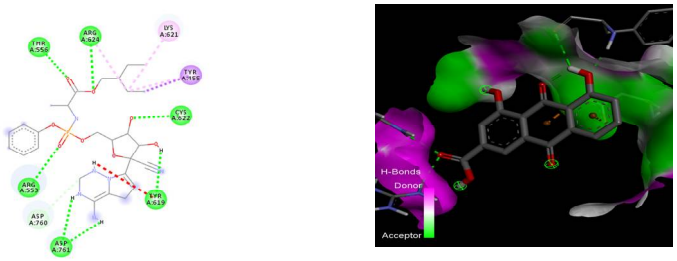

Figure 8. 2D & 3D Interactions of Rhein with the protein 6M71.

Table 5 Molecular docking analysis of the tested compounds against COVID-19 protein 6M17

Sl No.	Compound	PubChem CID	Binding energies (Kcal/mol)
1	Remdesivir	121304016	-7.7
2	Rhein	10168	-15.1
3	Glycyrrhizin	3495	-11
4	Lycorine	72378	-10.6
5	Clivocine	-	-10.5
6	Kaempferol 3-O-Rutinoside	122173234	-9.7
7	Theaflavin Digallate	5748168	-9.7
8	Cliviahaksine	-	-9.7
9	Nictoflorin	5318767	-9.6
10	Kaempferol 3-O-Robinobioside	15944778	-9.6
11	Diosmin	5281613	-9.6
12	Mimusopic Acid	6712545	-9.6
13	Clivocine	-	-10.5
14	α-Glucosyl Hesperidin	91972173	-9.3
15	Saikosaponins	167928	-9.3
16	Cynaropicrin	119093	-9.1
17	Ursolic Acid	64945	-9
18	Oleanolic Acid	10494	-9
19	β-Sitosterol	222284	-8.9
20	Gedunin	3458	-8.8
21	Nobilisine	12303691	-8.7
22	Clivacetine	-	-8.4
23	Silybin	31553	-8.2
24	Berberine	2353	-8.1
25	Triptofordin C-2	13874096	-8

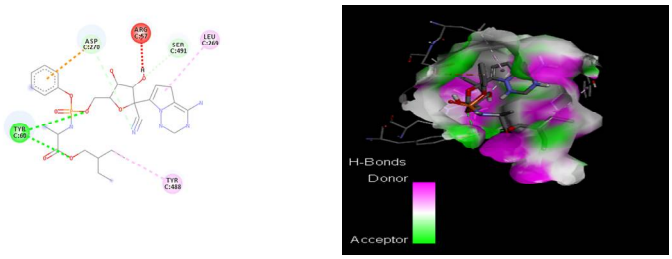

Figure 9. 2D & 3D Interactions of Remdesivir with the protein 6M17.

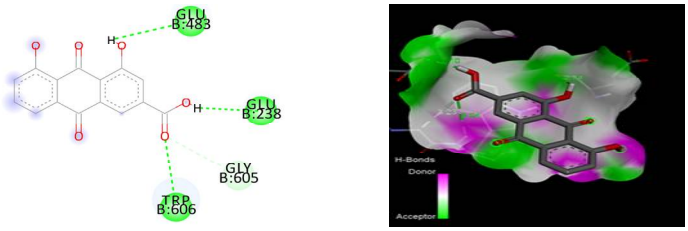

Figure 10. 2D & 3D Interactions of Rhein with the protein 6M17.

DISCUSSION

According to the above results, Camelliatannin H was found to have the highest molecular weight of 1567.116 g, lowest was Phosphoric acid with 97.98 g. Similarly, the surface area of the phytochemicals: were between 28.307 and 615.749. Octacosanol has the highest lipophilicity of 10.1412, while α-glucosyl hesperidin has the least lipophilicity of -3.3324.

The predicted absorption properties of the showed that β-sitosterol has the highest water solubility value of -7.121 while Pyrrolizin-1,7- dione-6- carboxylic acid, methyl(ester) has the lowest value of -1.143. Methyl eugenol has the highest permeability value of 1.732, but Nictoflorin having the least permeability value of 0.189. Likewise, triptofordin C-2, ursolic acid and Gedunin can be readily absorbed by the intestinal cells (100%) whereas Nictoflorin may not be absorbed intestine.

In In-silico prediction of in-vivo distribution of the phytochemicals, All the phytochemicals tested have relatively low steady-state volume of distribution. Also, the predicted result revealed Pyrrolizin-1, 7-Dione-6- carboxylic acid, methyl (ester) has the highest unbound fraction in the human blood. All the phytochemicals have relatively low blood–brain barrier and CNS permeability values. The In-silico metabolic studies showed that all the phytochemicals were metabolized in either of the cytochromes. The predicted clearance of each of the phytochemicals disclosed that Chebulagic acid has the highest total clearance rate of -2.638 while silybin has the least clearance rate of -0.001. The predicted toxicological profile of all the tested phytochemicals and has no mutagenic potentials against bacteria (AMES toxicity) but vernodalol and vernodalin could be toxic to bacteria. None of the phytochemicals has adverse effects on the hepatic or dermal cells. The phytochemicals are not inhibitors of human ether-a-go-go-related gene (hERG) hERG I and hERG II except veronicoside a may inhibit hERG II. All the phytochemicals have relatively low maximum recommended tolerated dose values.

CONCLUSION

The binding affinities of phytochemical Rhein were found to be better than those of remdesivir, with remdesivir having a binding affinity of -7.9 and Rhein having a binding affinity of -15.1, 4MM3 having a binding affinity of -7.2 and Rhein having a binding affinity of -9.8, 2GHV having a binding affinity of -7.2 and Rhein having a binding affinity of -12.4, 6M71 having a binding affinity of -8.1 The molecular characteristics of the phytochemicals employed in this investigation were determined. All the studied phytochemicals have the same expected toxicological profile and have no mutagenesis potential against bacteria (AMES toxicity), although vernodalol and vernodalin may be toxic to bacteria. The hepatic and cutaneous cells are unaffected by any of the phytochemicals. Except for veronicoside A, which may inhibit hERG II, none of the phytochemicals are inhibitors of human ether-a-go-go-related gene (hERG) I and II. The maximum suggested tolerable dosage levels for all phytochemicals are relatively modest. Following additional *in-vitro* and *in-vivo* assessment, we believe that the phytochemicals provided have greater and similar antiviral activity than remdesivir and can be utilized as an alternative to remdesivir as an antiviral medication to treat COVID-19.

ACKNOWLEGEMENT
We the authors acknowledge College of Pharmaceutical Sciences, Dayananda Sagar University for providing the facilities to carry out the above research.

CONFLICT OF INTEREST
We the authors do not have any conflict of interest.

REFERENCES
1. Abdelli, I., Hassani, F., Bekkel Brikci, S., & Ghalem, S. (2021). In silico study the inhibition of angiotensin converting enzyme 2 receptor of COVID-19 by Ammoides verticillata components harvested from Western Algeria. *Journal of Biomolecular Structure and Dynamics;* 39(9), 3263–3276. https://doi.org/10.1080/07391102.2020.1763199
2. Abou Baker, D. H., Amarowicz, R., Kandeil, A., Ali, M. A., & Ibrahim, E. A. (2021). Antiviral activity of Lavandula angustifolia L. and Salvia officinalis L. essential oils against avian influenza H5N1 virus. *Journal of Agriculture and Food Research;* 4, 100135. https://doi.org/10.1016/j.jafr.2021.100135
3. Akram, M., Tahir, I. M., Shah, S. M. A., Mahmood, Z., Altaf, A., Ahmad, K., Munir, N., Daniyal, M., Nasir, S., & Mehboob, H. (2018). Antiviral potential of medicinal plants against HIV, HSV, influenza, hepatitis, and coxsackievirus: A systematic review. *Phytotherapy Research;* 32(5), 811–822. https://doi.org/10.1002/ptr.6024
4. Andrys, D., Kulpa, D., Grzeszczuk, M., & Białecka, B. (2018). Influence of jasmonic acid on the growth and antimicrobial and antioxidant activities of Lavandula angustifolia Mill. Propagated in vitro. *Folia Horticulturae;* 30(1), 3–13. https://doi.org/10.2478/fhort-2018-0001
5. Astani, A., Reichling, J., & Schnitzler, P. (2010). Comparative study on the antiviral activity of selected monoterpenes derived from essential oils. *Phytotherapy Research;* 24(5), 673–679. https://doi.org/10.1002/ptr.2955
6. Bhuiyan, F. R., Howlader, S., Raihan, T., & Hasan, M. (2020). Plants Metabolites: Possibility of Natural Therapeutics Against the COVID-19 Pandemic. *Frontiers in Medicine;* 7, 444. https://doi.org/10.3389/fmed.2020.00444
7. de Sá, É. R. A., Costa, A. N., Costa, R. K. M., Souza, J. L., Ramos, R. M., & Lima, F. das C. A. (2021). In silico study of the interactions of Pilocarpus microphyllus imidazolic alkaloids with the main protease (Mpro) of SARS-CoV-2. *Molecular Simulation;* 47(1), 74–87. https://doi.org/10.1080/08927022.2021.1873321
8. Elmorsy, M. A., El-Baz, A. M., Mohamed, N. H., Almeer, R., Abdel-Daim, M. M., & Yahya, G. (2021). In silico screening of potent inhibitors against COVID-19 key targets from a library of FDA-approved drugs. *Environmental Science and Pollution Research;* https://doi.org/10.1007/s11356-021-16427-4
9. Jassim, S. A. A., & Naji, M. A. (2003). Novel antiviral agents: A medicinal plant perspective. *Journal of Applied Microbiology;* 95(3), 412–427. https://doi.org/10.1046/j.1365-2672.2003.02026.x
10. Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N., Bi, Y., Ma, X., Zhan, F., Wang, L., Hu, T., Zhou, H., Hu, Z., Zhou, W., Zhao, L., Tan, W. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet;* 395(10224), 565–574. https://doi.org/10.1016/S0140-6736(20)30251-8
11. Mohanraj, K., Karthikeyan, B. S., Vivek-Ananth, R. P., Chand, R. P. B., Aparna, S. R., Mangalapandi, P., & Samal, A. (2018). IMPPAT: A curated database of Indian Medicinal Plants, Phytochemistry and Therapeutics. *Scientific Reports*; 8(1). https://doi.org/10.1038/s41598-018-22631-z
12. Moses, T., & Goossens, A. (2017a). Plants for human health: Greening biotechnology and synthetic biology. *Journal of Experimental Botany;* 68(15), 4009–4011. https://doi.org/10.1093/jxb/erx268
13. Moses, T., & Goossens, A. (2017b). Plants for human health: Greening biotechnology and synthetic biology. *Journal of Experimental Botany;* 68(15), 4009–4011. https://doi.org/10.1093/jxb/erx268
14. Pires, D. E. V., Blundell, T. L., & Ascher, D. B. (2015). pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. *Journal of Medicinal Chemistry;* 58(9), 4066–4072. https://doi.org/10.1021/ACS.JMEDCHEM.5B00104/SUPPL_FILE/JM5B00104_SI_001.PDF
15. Rastogi, S., Pandey, D. N., & Singh, R. H. (2020). COVID-19 pandemic: A pragmatic plan for ayurveda intervention. *Journal of Ayurveda and Integrative Medicine;* https://doi.org/10.1016/j.jaim.2020.04.002
16. Shetty, R., Ghosh, A., Honavar, S. G., Khamar, P., & Sethu, S. (2020). Therapeutic opportunities to manage COVID-19/SARS-CoV-2 infection: Present and future. *Indian Journal of Ophthalmology;* 68(5), 693–702. https://doi.org/10.4103/ijo.IJO_639_20
17. Shojaii, A., & Abdollahi Fard, M. (2012). Review of Pharmacological Properties and Chemical Constituents of Pimpinella anisum . *ISRN Pharmaceutics;* 2012, 1–8. https://doi.org/10.5402/2012/510795
18. Zumla, A., Chan, J. F. W., Azhar, E. I., Hui, D. S. C., & Yuen, K. Y. (2016). Coronaviruses-drug discovery and therapeutic options. *Nature Reviews Drug Discovery;* 15(5), 327–347. https://doi.org/10.1038/nrd.2015.37

CITATION OF THIS ARTICLE
Mahesh A R, Josephine L J, Veda B H. Repurposing of Isolated Phytochemicals for Its Antiviral Activity Against Sars Covid-19 Through In-Silico Evaluation. Bull. Env. Pharmacol. Life Sci., Vol 12 [7] June 2023: 227-234