



IJEAST

INTERNATIONAL JOURNAL
OF ENGINEERING APPLIED SCIENCE
AND TECHNOLOGY



VOLUME : 5 ISSUE : 6 Print / Issue Publication Date: 21-Dec-2020



ISSN : 2455-2143



DOI : 10.33564/IJEAST.2020.v05i06.047

Indexed In



WWW.IJEAST.COM

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DRUG DISCOVERY AGAINST COVID-19 FROM INDIAN MEDICINAL PLANTS – COMPUTATIONAL APPROACH

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Abstract— Coronavirus pandemic has caused an enormous misfortune for the worldwide economy just as worldwide wellbeing. Such cases show us the need to create vaccines against novel infections that continually develops with nature. Currently more than 200 potential candidate vaccines are in the preliminary stages, but not many of them has given some certain outcomes. The 3CL^{pro} sequence has a major involvement in the replication of the viral genome. Consequently, it goes about as an expected site for the anti COVID-19 medications. The current examination centers around screening the Indian medicinal plants and their heavy metal nanoparticle conjugates for their capacity to go about as a characteristic inhibitor for the infection.

Keywords— Iron Nanoparticles (FeNPs), Gold Nanoparticles (AuNPs), Zinc Nanoparticles (ZnNPs), Reverse Transcriptase Polymerase Chain Reaction (RT-PCR), Atomic Contact Energy (ACE)

I. INTRODUCTION

In 2019 a new strain of infection was distinguished that caused deadly respiratory ailment [Xu and Chen 2020]. WHO initially classified the virus as 2019 novel coronavirus (2019-nCoV) [Ji 2020]. Later, in January 2020 the primary genome sequence of the virus became accessible that provided an upper edge to the researchers to build a RT-PCR to distinguish the malady in affected patients [Ma et al. 2020]. As of 30th August 2020, according to WHO overall in excess of 24 million affirmed cases have been accounted for with in excess of 8 lakh deaths spreading across 216 nations. Recent investigations have proposed that Angiotensin Receptor 1 (ATR1) may prove advantageous for the individuals who get tainted with COVID-19 and face pneumonia like indications. Phadke and Saunik [Phadke and Saunik 2020] likewise proposed the conceivable utilization of ATR1 blockers to treat patients with COVID-19. Considering the way that these investigations are focusing on the likely utilization of ATR1 inhibitors comes from the perceptions that Angiotensin Converting Enzyme 2 (ACE2) acts as a main site for the docking of spike protein of SARS-CoV-2.

There are various literatures describing the taxonomy of coronavirus and categorizing it in the *Coronaviridae* family and *Coronavirinae* sub-family [Chen et al. 2020; Hu et al. 2018]. Despite the fact that the Sars-CoV-2 is ordered in beta-Coronavirus group, it is unique in relation to the MERS-CoV and SARS-CoV. Ongoing investigations have demonstrated that the SARS-CoV-2 shares a limited nucleotide identity and similarity with the SARS-CoV [Tao et al. 2020; Zhou et al. 2020]. The viruses placed in the beta-Coronavirus group usually generates 800 kDa polypeptide when their genome transcription occurs. The polypeptide generated is then cleaved in order to produce different proteins. The proteolytic disintegration of the polypeptide is governed by 3-Chymotrypsin-like protease (3CL^{pro}) and Papain-like protease (PL^{pro}). 3CL^{pro} is responsible for the segmentation of the polypeptide at 11 distinct places so that the viral proteins can be generated [Anand et al. 2003]. Homology modelling have revealed that 3CL^{pro} has highly conserved sequence. Several inhibitors of 3CL^{pro} have been discovered in past via high-throughput screening and rational drug design [Kumar et al. 2013; Kuo et al. 2015]. Hence, it is fair to consider that it can potentially act as an inhibitor for the coronavirus [Needle et al. 2015].

Tahir and group [Tahir et al. 2020] have exhibited a 3D homology model of the 3CL^{pro} sequence (PMDB ID: PM0082635) and screened it against the Chinese medicinal plants.

The worldwide pandemic circumstance has impelled various nations to act quickly and find a potential fix as an antibody against this fatal infection. At present in excess of 200 active candidate vaccines are in progress against the infection [Lurie et al. 2020]. The outcomes from two vaccine trials are accounted for, one from AstraZeneca upheld Jenner Institute at Oxford University [Folegatti et al. 2020] and the other from CanSino Biologics from Wuhan, China [Zhu et al. 2020]. Both of these vaccine trials have indicated positive outcomes in there 1/2 stage. Since the populaces scale was low and ethnic diversity was low [Bar-zeev and Moss 2020], we are still in a race to locate a superior fix. One potential approach to attempt to do this is to concentrate on the characteristic accessibility of the therapeutic components found in the nature. Indian



medicinal plants, particularly those that are utilized straightforwardly in a palatable manner has pulled in much consideration due to the naturally occurring bioactive components present in them.

Biosynthesized metal nanoparticles have shown significant antiviral activity [Kuppuswamy et al. 2016]. Silver oxide and gold nanoparticles synthesized using *Oscillatoria* sp. and *S. platensis*, respectively have inhibited the growth and replication of Herpes Simplex (HSV-1) [El-Sheek et al. 2020]. The bio-synthesized Silver nanoparticles from the plant extract of *Andrographis paniculata* and *Tinospora cordifolia* demonstrated a high antiviral behavior when screened against Chikungunya virus [Sharma et al. 2019]. Thus, there is a need to synthesize heavy metal nanoparticles to explore their antiviral properties.

Thus, the present study focusses on the screening of Indian medicinal plants and their heavy metal nanoparticle conjugates (Iron, Gold and Zinc) against the 3CL^{pro} sequence of Sars-CoV-2 virus in order to explore natural bioactive compounds having a potential to act as a natural inhibitor against the virus.

II. MATERIALS AND METHOD

A. Data Collection

A comprehensive phytochemical database was created containing major phytochemicals obtained from the Indian medicinal plants. While curating the data, we only targeted those Indian medicinal plants that are commonly used in the spices. These phytochemicals as well as their nanoparticle conjugates (Iron, Gold and Zinc) were screened against the 3CL^{pro} sequence of viral structure (PMDB ID: PM0082635) submitted by [Tahir et al. 2020].

B. Molecular Docking Studies

PatchDock online server was utilized for the docking studies. The structure of phytochemicals and heavy metals were downloaded from PubChem database. The details of the phytochemicals are given in Table 1. The 3CL^{pro} viral structure was download from PMDB database (PMDB ID: PM0082635). The nanoparticle conjugates of the respective phytochemicals were made using ChemOffice [ChemOffice 2002]. Ligands were energy minimized using Chem3D and the protein was energy minimized using Chimera [UCSF Chimera 2004]. The protein file was made clear by deleting the native ligand and the water molecules. As suggested by the tool, the RMSD value was fixed at <4Å. The result obtained were then visualized in Discovery studio.

III. RESULT AND DISCUSSION

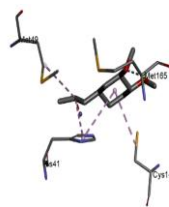
The molecular docking was carried out between the SARS-CoV-2 3CL^{pro} and the major phytochemicals of the medicinal plants and their nanoparticles. The GC-MS data of the medicinal plants were collected and the major phytochemicals were identified. We gathered 14 medicinal plants with the

possibility of their phytochemicals to act as a natural inhibitor against the SARS-CoV-2 3CL^{pro}. We made their respective nanoparticles with heavy metals such as Iron (FeNPs), Gold (AuNPs) and Zinc (ZnNPs). Out of the 14 plants, 5 FeNPs conjugate of the plants, 2 AuNPs conjugate of the plants and 2 ZnNPs conjugate of the plants showed the desired results. The results are shown in Table 2.

A. Iron Nanoparticles

The major phytochemicals of the 15 medicinal plants and their iron nanoparticle conjugates were docked against SARS-CoV-2 3CL^{pro}. Out of the 15 medicinal plants only 5 of them showed the desired results against the viral structure. The docking of FeNP with SARS-CoV-2 3CL^{pro} showed an unfavorable binding with Arg298 (figure 1a). Eugenol was identified as the major phytochemical in Pan (*Piper betel*) [Madhumita et al. 2019] and Clove (*Syzygium aromaticum*) [Srivastava et al. 2005]. The docking of eugenol with SARS-CoV-2 3CL^{pro} showed hydrophobic interaction with Met165 and Cys145 with a docking score of 3,132 and an ACE of -126.38kcal/mol (figure 1b). On the other hand, the docking of Eugenol conjugated with Iron (Eugenol-FeNP) showed a pi-donor hydrogen bonding with the His41 and hydrophobic interaction with Cys145 and His163 with a docking score of 3,528 and ACE of -98.25 kcal/mol which was higher than eugenol alone (figure 1c). Thymol was identified as the major phytochemical found in Ajwain (*Trachyspermum ammi* L) [Dhaiwal et al. 2017]. Docking analysis of thymol with SARS-CoV-2 3CL^{pro} showed hydrophobic interactions with His41, Cys145, His163, Met165 and Met49 with a docking score of 3,082 and ACE of -126.41 kcal/mol (figure 1d). The docking of thymol conjugated with iron (Thymol-FeNP) showed carbon hydrogen bonding with Asn142 and hydrophobic interactions with Met49, Cys145, Met165 and His41 with a docking score of 3,254 and ACE of -48.84 kcal/mol which was higher than thymol alone. Also, the iron ion showed metal acceptor bonding with Leu141 (figure 1e). Carvone was identified as the major phytochemical in Corn Mint (*Mentha arvensis*) [Balasubramanian et al. 2016]. The docking of carvone with the viral structure showed hydrophobic interactions with Met6, Arg298 and Phe8 and a restricted binding with Ser123 with a docking score of 3,100 and an ACE of -120.57 kcal/mol (figure 1f). The docking of carvone conjugated with iron (Carvone-FeNP) showed carbon hydrogen bonding with Asn142 and hydrophobic interactions with Met49, Met165, Cys145 and His41 with a docking score of 3,356 and an ACE of -64.93 kcal/mol which was more than carvone alone. The iron ion also showed metal acceptor bonding with Leu141 and Ser144 (figure 1g). Methyl isoeugenol was identified as the major phytochemical in Tulsi (*Ocimum sanctum*) [Balasubramanian et al. 2014]. The docking of methyl isoeugenol with SARS-CoV-2 3CL^{pro} showed hydrophobic interactions with Cys145 and His163 and a restricted interaction with Glu166 with a docking score of 3,440 and an ACE of -125.25 kcal/mol (figure 1h). The

docking of methyl isoeugenol conjugated with iron (Methyl isoeugenol-FeNP) showed carbo hydrogen bonding with Met165 and hydrophobic interactions with Cys145, Met49 and His41 with a docking score of 3,584 and an ACE of -103.34 kcal/mol which was more than methyl isoeugenol alone (figure 1i). Thus, this study suggests that the iron conjugates of the respective phytochemicals showed better binding affinity than their respective phytochemical part. Thus, there is a possibility that the nanoparticle conjugates of the respective phytochemicals might prove beneficial in the form of natural inhibitor against SARS-CoV-2 3CL^{PRO}.

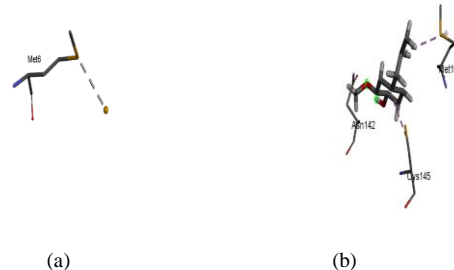
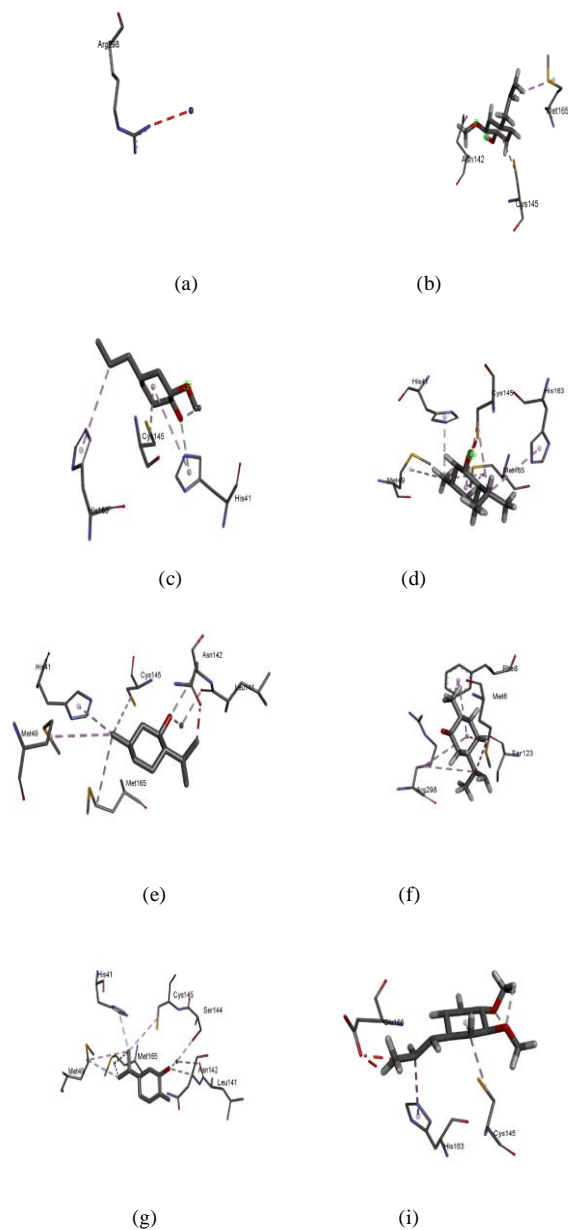


(i)

Fig. 1. Docking analysis of SARS-CoV-2 3CL^{PRO} with (a) FeNP (b) Eugenol (c) Eugenol-FeNP (d) Thymol (e) Thymol-FeNP (f) Carvone (g) Carvone-FeNP (h) Methylisoeugenol (i) Methylisoeugenol-FeNP

A. Gold Nanoparticles

The phytochemicals of 15 medicinal plants and their gold nanoparticle (AuNPs) conjugate were docked with SARS-CoV-2 3CL^{PRO}. The docking of AuNP with SARS-CoV-2 3CL^{PRO} showed a metal acceptor binding with Met6 (figure 2a). Out of 15 plants only 2 showed desire results. Eugenol, the major phytochemical of Pan (*Piper betel*) [Madhumita et al. 2019] and Clove (*Syzygium aromaticum*) [Srivastava et al. 2005] when docked with SARS-CoV-2 3CL^{PRO} showed hydrophobic interactions with Cys145 and Met165 and a restricted interaction with Asn142 with a docking score of 3,132 and an ACE of -126.38 kcal/mol (figure 2b). On the other had the docking of eugenol conjugated gold nanoparticle (Eugenol-AuNP) showed hydrogen bonding with Glu166, carbon hydrogen bonding with Phe140 and hydrophobic interactions with Cys145, Leu27, and His41 with a docking score of 3,332 and an ACE of -105.83 kcal/mol which was more than eugenol alone (figure 2c). The gold ion showed metal acceptor bonding with Glu166. Thus, this study suggests that the gold conjugate of eugenol (Eugenol-AuNP) shows better binding than eugenol alone and can possibly act as a natural inhibitor for the viral structure.



(a) (b)

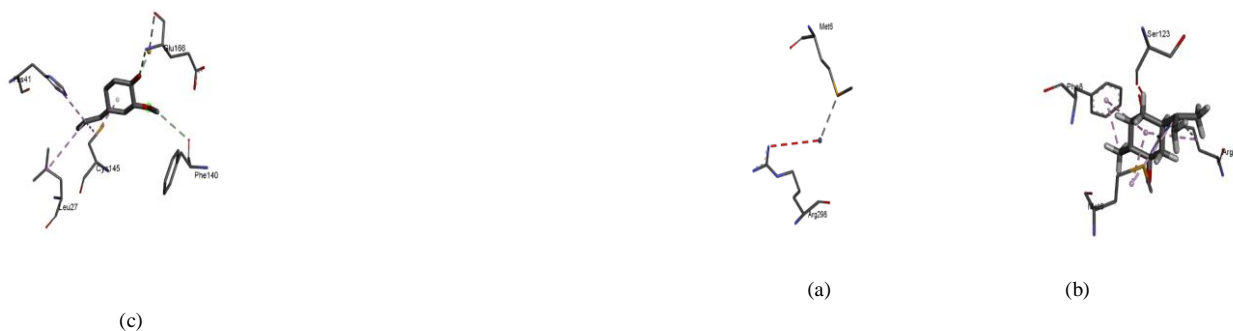


Fig. 2. Docking analysis of SARS-CoV-2 3CL^{pro} with (a) AuNP (b) Eugenol (c) Eugenol-AuNP

B. Zinc Nanoparticles

Out of 15 medicinal plants, only 2 of them showed the desired results. The docking of ZnNPs with SARS-CoV-2 3CL^{pro} showed a metal acceptor binding with Met6 and a restricted binding with Arg298 (figure 3a). Carvone was identified as the major phytochemical present in Corn Mint [Balasubramanian et al. 2016]. The docking of carvone with SARS-CoV-2 3CL^{pro} showed hydrophobic interactions with Met6, Arg298 and Phe8 along with a restricted interaction with Ser123 with a docking score of 3,100 and an ACE of -120.57 kcal/mol (figure 3b). The docking of zinc conjugate of carvone (Carvone-ZnNPs) showed hydrogen bonding with His41, His164 and Met165. It also showed hydrophobic interactions with Met165, Met49, Cys145 and His163 with a docking score of 3,246 and an ACE of -125.18 kcal/mol which was more than carvone alone (figure 3c). The zinc ion of Carvone-ZnNPs also showed metal acceptor interaction with His41. Linalyl acetate was identified as the major phytochemical of Lavender [Negi et al. 2015]. Docking of Linalyl acetate with SARS-CoV-2 3CL^{pro} showed hydrophobic interactions with Met49, Cys145, His41 and His163 with a docking score of 3,850 and an ACE of -113.34 kcal/mol (figure 3d). The zinc conjugate of Linalyl acetate (Linalyl acetate-ZnNPs) showed hydrogen bonding with Cys145 and His163. It also showed hydrophobic interactions with Cys145, Met49, His41 and His163 with a docking score of 3,864 and an ACE of -130.30 kcal/mol (figure 3e) which was lightly more than Linalyl acetate alone. The zinc ion also showed an electrostatic attractive interaction with Glu166. The zinc conjugates of carvone (Carvone-ZnNPs) and Linalyl acetate (Linalyl acetate-ZnNPs) showed better binding than their phytochemical counterpart. The nanoparticles conjugates might have a possibility to act as a natural inhibitor against SARS-CoV-2 3CL^{pro}.

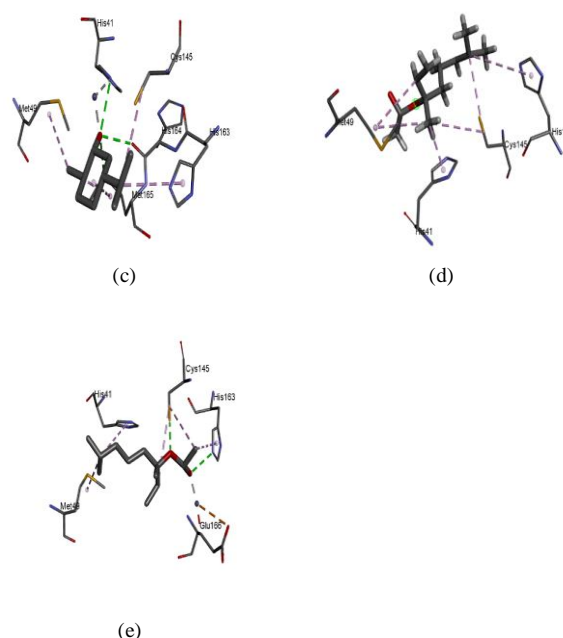


Fig. 3. Docking Analysis of SARS-CoV-2 3CL^{pro} with (a) ZnNP (b) Carvone (c) Carvone-ZnNPs (d) Linalyl acetate (e) Linalyl acetate-ZnNPs

Table -1 Plants and their respective phytochemicals with PubChem CID

Plants	Phytochemicals	PubChem CID
Ajwain (<i>Trachyspermum ammi</i> L.)	Thymol [Dhaiwal et al. 2017]	6989
Aloe vera (<i>Aloe vera</i> L)	Hexadecanoic acid [Bawankar et al. 2012]	985
Cinnamon (<i>Cinnamomum burmanii</i>)	Trans-cinnamaldehyde [Anshory and Nugraha 2017]	637511
Clove (<i>Syzygium aromaticum</i>)	Eugenol [Srivastava et al. 2005]	3314
Coriander (<i>Coriandrum</i>)	Geranyl acetate [Pande et el.	1549026



<i>sativum</i> L)	2010]	
Corn Mint (<i>Mentha arvensis</i>)	Carvone [Balasubramanian et al. 2016]	7439
Fenugreek (<i>Trigonella foenum-graecum</i>)	Cholestan-3-ol [Kumaravel et al. 2017]	10992748
Ginger (<i>Zingiber officinale</i>)	Zingiberene [Taylor et al. 2013]	92776
Henna (<i>Lawsonia inermis</i> L)	Acetic acid [Mengoni et al. 2015]	176
Lavender (<i>Lavandula angustifolia</i>)	Linalyl acetate [Negi et al. 2015]	8294
Lemongrass (<i>Cymbopogon citratius</i>)	Citral [Ali et al. 2017]	638011
Pan (<i>Piper betel</i>)	Eugenol [Madhumita et al. 2019]	3314
Tulsi (<i>Ocimum sanctum</i>)	Methyl isoeugenol [Balasubramanian et al. 2014]	637776
Turmeric (<i>Curcuma longa</i>)	Curcumin [Tennyson et al. 2019]	969516

Table 1 show the plants and their respective major phytochemicals along with their PubChem CID which were screened against the SARS-CoV-2 3CL^{pro} viral structure.

Table 2 – Protein, Ligands and their Docking Score and ACE

Protein	Ligand	PatchDock Score	ACE (kcal/mol)
SARS-CoV- 2 3CL ^{pro}	Iron (FeNP)	1102	34.54
SARS-CoV- 2 3CL ^{pro}	Eugenol	3132	-126.38
SARS-CoV- 2 3CL ^{pro}	Eugenol+FeNP	3528	-98.25
SARS-CoV- 2 3CL ^{pro}	Carvone	3100	-120.57
SARS-CoV- 2 3CL ^{pro}	Carvone+FeNP	3356	-64.93
SARS-CoV- 2 3CL ^{pro}	Methylisoeugenol	3440	-125.25
SARS-CoV- 2 3CL ^{pro}	Methylisoeugenol+Fe NP	3584	-103.34
SARS-CoV- 2 3CL ^{pro}	Thymol	3082	-126.41
SARS-CoV- 2 3CL ^{pro}	Thymol+FeNP	3254	-48.84

SARS-CoV- 2 3CL ^{pro}	Gold (AuNP)	470	0
SARS-CoV- 2 3CL ^{pro}	Eugenol+AuNP	3332	-105.83
SARS-CoV- 2 3CL ^{pro}	Cholestan-3-ol	5492	-234.24
SARS-CoV- 2 3CL ^{pro}	Cholestan-3-ol+AuNP	5448	-226.35
SARS-CoV- 2 3CL ^{pro}	Zinc (ZnNPs)	470	0

Table 2 shows the viral protein and the ligands it was docked with that showed desirable results. The table also depicts the PatchDock Score and the Atomic Contact Energy (ACE).

IV. CONCLUSION

The current study focused on exploring the anti-viral activity of the major phytochemicals present in the Indian medicinal plants. These medicinal plants were selected due to their common usage in the Indian spices. Thus, there might be a possibility that their natural phytochemicals can provide immunity against the viral infection. These naturally occurring phytochemicals were then conjugated with heavy metal ions such as Iron (Fe), Gold (Au) and Zinc (Zn) in order to make their nanoparticle counterpart. The phytochemicals and their nanoparticle conjugates were then docked against the 3CL^{pro} sequence of the viral structure to see their interaction. Cys145 and His41 together act as a catalytic dyad in the viral structure. We hypothesized that the phytochemicals and their nanoparticle conjugates might interact with the catalytic dyad of the viral structure and thereby act as a natural inhibitor of the viral infection. The present study demonstrated that the 7 naturally occurring phytochemicals showed the desired binding with the active site of the viral structure and 5 iron nanoparticle conjugate, 2 gold nanoparticle conjugate and 2 zinc nanoparticle conjugates gave the desired results. Although, the present study only focused on the molecular docking aspect of the viral structure and the phytochemicals, this study opens up a new domain to try and synthesize drugs from these medicinal plants using the pharmacophore modelling in order to create natural inhibitors against the virus.

ACKNOWLEDGEMENT

The authors would like to acknowledge Ms. Sneha Kapse and Mr. Avishek Paul for their valuable feedback and proofreading the manuscript.

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