Molecular docking and simulation investigation: effect of beta-sesquiphellandrene with ionic integration on SARS-CoV2 and SFTS viruses

Amit Joshi, G. Sunil Krishnan and Vikas Kaushik

Abstract

Background: At present, viral diseases become major concern for the world. SARS-CoV2 and SFTS viruses are deadly in nature, and there is a need for developing best treatments for them. Modern in silico approaches were found to be very handy in determining putative drug molecules. In this study, we analyze interaction of beta-sesquiphellandrene (compound belongs to ginger) with spike protein (Sp) and membrane glycoprotein polyprotein (MPP).

Results: Our molecular docking and simulation study reveals the perfect binding pocket of Sp and MPP holding beta-sesquiphellandrene (bS). Binding energies for MPP-bS and Sp-bS were found to be −9.5 kcal/mol and −10.3 kcal/mol respectively. RMSD and RMSF values for docked complexes were found to be in selectable range, i.e., 1 to 3 Å and 1 to 8 Å respectively. Modern computational tools were used here to make this investigation fast and effective. Further, ADME analysis reveals the therapeutic validations for beta-sesquiphellandrene to act as a useful pharmaactive compound. Beta-sesquiphellandrene provides not only inhibitory effect on spike protein of SARS-CoV2 but also similar inhibitory effects on membrane glycoprotein polyprotein complex of SFTS virus, which hampers the pathological initiation of the diseases caused by both the viruses, i.e., COVID-19 and severe fever with thrombocytopenia syndrome.

Conclusion: This method of computational analysis was found to be rapid and effective, and opens new doors in the domain of in silico drug discovery. Beta-sesquiphellandrene can be used as effective medicine to control these harmful pathogens after wet lab validations.

Keywords: SARS-CoV2, SFTS, Beta-sesquiphellandrene, Docking, Simulation

Background

Traditional therapy for controlling cough-cold problems with fast recovery includes mixture of ginger and jaggery. Latest studies supported such treatment strategies or home remedies for antiviral effects; it was observed that the Chinese also used same contemporary medications, like Ge Gen Tang (consist of ginger and a sweet kudzu roots) [1, 2]. Ginger holds wonderful therapeutic properties and investigated by numerous scientific researches globally, especially from India, China, and Pakistan. Ginger consists of many therapeutic chemicals, additionally been accounted in modern researches. In 1994, Dr. C V Denyer and collaborators [3] conducted 12 significant investigations on the restorative properties of ginger. A portion of these highlight its antioxidative properties, some show it to have anti-inflammatory impacts, some to its capacity to treat queasiness, a couple to its anti-emetic capacity, and there is even a paper from the West Asian area recommending that it might...
have a helpful impact against dementia and Alzheimer’s. Also, latest reports have explored the current proof on a few properties of ginger in wellbeing and physical movement, including its anti-malignancy properties [4]. Ginger has 6-gingerol and 6-paradol and enhances 5-fluorouracil efficiency to show anti-cancerous properties [5]. Ginger (Zingiber officinale) contains a very crucial anti-viral compound beta-sesquiphellandrene [6]. Prior work by Denyer and collaborators extracted compound called beta-sesquiphellandrene from ginger which holds antiviral capacity and defeats the infection caused by common cold virus [3]. Jaggery a nutritive product obtained from sugarcane holds nutritive elements sugar, calcium, iron, phosphorus, and magnesium [7].

In this study, we tried to integrate ions and beta-sesquiphellandrene by in silico methods and analyze its interaction with Spike protein (Sp) [8] of SARS-CoV2 and membrane glycoprotein polyprotein (MGp) [9] of SFTS virus. Both of these proteins belong to viral domain and have a role in access to human cytological areas, particularly targeting respiratory surfaces. Spike protein plays a major role in interaction to ACE2 receptors of endothelial cells surrounding pulmonary region to bring entry of SARS-CoV2 [10], while membrane glycoprotein polyprotein plays a major role in entry to thrombocytes [11]. SFTS virus has membrane glycoprotein polyprotein complex [12], which attaches to myosin heavy chain peptides, clathrin protein, and sorting nixin-11 protein of host cellular domains. Myosin heavy chain proteins and clathrin coat proteins play a major role during internalization of SFTS viruses during endosomal formation, whereas sorting nixin-11 proteins of host side play crucial role during transfer of viral entities from endosomes to cytoplasm [13]. SFTS as well as SARS-CoV2 viruses are zoonotic in nature. SARS-CoV2 is a novel virus of family coronaviridae, which is transmitted from bats and causes COVID-19 disease. Other potential hosts that are responsible for transmitting SARS-CoV2 to humans can be categorized into wild animals and domestic animals. Wild animal's category includes intermediate hosts like pangolins, turtles, snakes, and ferrets [14, 15]. Earlier domestic animals like poultry, dogs, and cats were thought to be underlined as intermediate hosts for SARS-CoV2 transmission, but later developments suggested that the fast antibody synthesis against SARS-CoV2 in these organisms makes them immunized from harmful consequences [14, 16]. SFTS is a novel phlebovirus of family Bunaviridae, which is transmitted from ticks and causes severe fever with thrombocytopenia. SFTS (severe fever with thrombocytopenia syndrome) virus, thrombocytes are primary target for this virus, causes extreme deadly hemorrhagic fever [17–19]. SARS-CoV2 and COVID-19 pandemic are the most studied in recent researches and responsible for affecting the respiratory system [20]. Mode of infection for both viruses is primarily by air-droplet transmission; in Fig. 1, interaction of SARS-CoV2 and SFTS virus with human physiological systems is presented. SFTS virions target the lymphatic system, primarily spleen to target killing of monocytes and thrombocytes (platelets) [21]. SARS-CoV2 targets ACE receptors to make entry in endothelial cell [22] while SFTS virions target lymphoid tissues particularly thrombocytes [23].

Our study involves ADME analysis, molecular docking, and molecular dynamics and simulation study for investigating interaction of beta-sesquiphellandrene associated with ions to Sp of SARS-CoV2 and MGp of SFTS virus to reveal its therapeutic properties. Molecular docking studies assisted in revealing binding pockets within protein molecules where beta-sesquephellandrene can interact. To validate the interactions between ligand and protein receptors of viruses, we conducted molecular dynamic simulation studies successfully. It is very novel, fast, and effective method that can be applied for futuristic computer-based drug designing and discovery.

Methods

ADME analysis
ADME (adsorption, distribution, metabolism, and excretion) analysis for beta-sesquiphellandrene was conducted by using the Swiss-ADME server (http://www.swissadme.ch/) [24]. ADME analysis assisted in identifying druglikeness based on Lipinski rule of five [25]; this rule states that suitable or orally active drug must possess no more than 5 hydrogen bond donors (N–H, O–H bonds), no more than 10 hydrogen bond acceptors (all nitrogen, oxygen atoms), molecular mass less than 500 Da, an octanol-water partition coefficient, i.e., log \( P \leq 5 \), and number of rotational bond should be less than 10. This rule allows best drugs to possess at least any 4 of the abovementioned characters or one can simply say that chemicals to be in selection criteria of good oral drugs are only allowed to do any single Lipinsiki violation not more than that.

Structural retrieval
Structures for spike protein (Sp) and membrane glycoprotein polyprotein (MPp) were retrieved from the RCSB PDB server (https://www.rcsb.org/search). Drug (beta-sesquiphellandrene) structure was retrieved from the PubChem server (https://pubchem.ncbi.nlm.nih.gov/ ) in sdf format, and then converted to pdb format by deploying the Open Babel software [26].

Molecular docking
Docking studies were conducted to analyze interaction between protein and drug molecules. Retrieved
molecules were subjected to the PatchDock server [27] and further directed to FireDock screening. PatchDock servers are free and allow users to dock ligands with proteins (receptors), and FireDock a utility within this server assists users to screen out the best possible complexes from thousands of docked complexes. It also provides an ACE value (atomic contact energy) for docked complexes along with a visual interpretation of interaction of ligand within binding pocket of protein. Further, the PyMOL software [28] was used to check hydrogen bonds between ligand and protein and to reveal binding pocket; this always confirms the interaction based on bond length and binding energy. Binding energies were calculated by redocking with the AutoDock Vina tool [29].

**MD simulation**
MD simulation was conducted by deploying GROMACS [30], a Linux-based free simulation tool. MD simulation analysis of 100 ns was performed for the complex with drug and the protein molecules deploying Amber Force Field in GROMACS. The docked complexes were protonated, and counter particles (sodium ions) were added properly to make the absolute charge zero. The atoms were solvated utilizing TIP3PBOX water model with the edge of the octahedral box 10 Å away from solute particles. All through the reenactment, every complex framework is kept at the temperature of 300 K with consistent pressure. Energy minimization was accomplished for 50,000 steps.

**Results**
**Beta-sesquiphellandrene: ADME analysis**
Beta-sesquiphellandrene \(((3R)-3-[\(2S\)-6-methylhept-5-en-2-yl]-6-methylidenecyclohexene)\) was found to have a molecular weight of 204.35 g/mol; it does not have hydrogen bond donors and acceptors; it consists of 4 rotatable bonds, topological surface area 0 Å², and single Lipinski violation. Gastrointestinal absorption is low and zero blood-brain permeability. Easy to be removed during excretion as it shows interaction with cytochrome p450 during xenobiotic metabolism and does not show inhibition of CYP1A2 isozyme. All characteristics reveal it to be a potent putative drug candidate. In Fig. 2, its 3D structure and all ADME properties are presented.

**Structure retrieval**
PubChem chemical ID for beta-sesquiphellandrene is 12315492, which was used to access its 3D structure in sdf format. Then, this file was converted to pdb by deploying the Open Babel tool. Structure for spike protein (Sp) and membrane glycoprotein polyprotein (MPP) was downloaded from the RCSB-PDB server. PDB ID for

---

**Fig. 1** Basic pathology of viruses (host-virus interaction): SARS-CoV2 attachment with ACE2 receptors of endothelial cells and SFTSV clustered in endosomes with the help of clathrin-coated proteins.
**Fig. 2** ADME analysis of beta-sesquiphellandrene along with its three dimensional structure

**Fig. 3** Structure of proteins. **a** Spike protein of SARS-CoV2. **b** Membrane glycoprotein polyprotein of SFTS virus
spike protein is 2GHW and for membrane glycoprotein polyprotein is 5Y11. Figure 3 presents the structure of both proteins.

Molecular docking analysis
Docking studies assisted in determining ACE values for both the perfectly docked models. Membrane glycoprotein polyprotein interacting with beta-sesquiphellandrene results in complex MPp-bS, found to have ACE value $-250$ and binding energy $-9.5$ kcal/mol. Spike protein interacts with beta-sesquiphellandrene resulting in formation of complex Sp-bS, found to have ACE value $-265$ and binding energy $-10.3$ kcal/mol. Hydrogen bond interactions were also revealed during this course of investigation. In Fig. 4, both the docked models are presented, indicating hydrogen bond formation between drug molecule and protein molecule. Spike protein interacting with beta-sesquiphellandrene (Sp-bS): Leu 504, Leu374, and Lys373, makes binding pocket also exhibit 2.5 Å, 2.7 Å, and 3.2 Å hydrogen bonds respectively. Membrane glycoprotein polyprotein interacting with beta-sesquiphellandrene (MPp-bS): Asp168, Ser169, and Lys170, makes binding pocket also exhibit 2.8 Å, 2.3 Å, and 2.5 Å hydrogen bonds respectively. In Table 1, molecular docking and hydrogen bond analysis for docked models is given.

MD-Simulation analysis
Molecular dynamics and simulation studies reveal stability of interactions in docked complexes. Trajectory analysis reveals root mean square deviation (RMSD) and root mean square fluctuation (RMSF) plots generated for both the docked models presented in Fig. 5. RMSD values were found to be in suitable range of 1 to 3 Å, and RMSF values were found to be in suitable range in 1 to 8 Å, for MPp-bS and Sp-bS docked complexes. An MD simulation study clearly indicates slow interaction changes in a long run of 100 ns.

MD simulation study reveals that beta-sesquiphellandrene molecule can successfully interact with MPp and Sp proteins to form stable complex. Beta-sesquiphellandrene is easily available as a natural food (ginger) from ancient times, and its easy availability makes it a promising source for future regimen development. This new computational approach was found to be fast and easy for drug discovery and opens new research dimensions.

Discussion
SARS-CoV2 spike protein interacts with ACE (angiotensin-converting enzyme), to get internalized to endothelial cell. Later, SARS-CoV2 multiplies within different cells and cause not only respiratory problems but also neuropathy [31]. SFTS virus interacts with lymphoid tissue and causes immune system damages. This resulted to leukocytopenia (reduction in WBCs number) and thrombocytopenia (reduction in thrombocytes number) [32]. Beta-sesquiphellandrene was found to have perfect interaction with spike protein of SARS-CoV2 and membrane glycoprotein polyprotein of SFTS virus. SFTS virus causes asymptomatic effects like SARS-CoV2 in patients [33, 34]. SFTS virus has membrane glycoprotein polyprotein complex [12], which attaches to myosin heavy chain peptides and clathrin protein during internalization via endosomes, whereas sorting nexin-11 proteins of host side play crucial role during transfer of viral entities from endosomes to host cytoplasm [13]. Many molecular docking and molecular simulation-based studies
were found to be successful in determining therapeutic peptide-based epitopes for controlling Dengue virus [35], SARS-CoV2 [10], Zika virus [36], and Whipple’s disease caused by bacterium *Tropheryma whipplei* [37]. Binding energies for MPp-bS and Sp-bS were found to be $-9.5$ kcal/mol and $-10.3$ kcal/mol respectively. An RMSD and RMSF value was found to be in suitable range and indicates perfectly stable interaction between ligand and proteins under consideration. Recent study on drug discovery against SARS-CoV2 for predicting drugs like remdesivir, ribavirin, sofosbuvir, galidesivir, and tenofovir were based on molecular docking and simulation-based analysis, and later, wet lab analysis makes such predictions to be fruitful in some extent [38]. Similarly, drug repurposing of lopinavir, oseltamivir, and ritonavir binding with SARS-CoV2 proteins to achieve successful treatment strategies was also based on computational analysis including docking and simulation strategies [39]. A recent study also reveals the importance of membrane glycoprotein polyprotein of SFTS virus in viral entry via membrane fusion [40]; still there is less availability of any computational-based drug discovery against this harmful virus. SARS-CoV2 started to spread from Wuhan, China, and at present caused more than 0.7 million deaths all around the globe. Ginger is a natural product and easily available to everyone for home remedy. Essential oils of medicinal importance having beta-sesquiphellandrene possess anti-viral and

| Docked complex                                      | ACE value | Binding energy (kcal/mol) | Amino acid residues of proteins/hydrogen bond length (Å) |
|-----------------------------------------------------|-----------|---------------------------|--------------------------------------------------------|
| Spike protein and beta-sesquiphellandrene (Sp-bS)  | $-265$    | $-10.3$                   | Leu504 (2.5 Å) Leu374 (2.7 Å) Lys343 (3.2 Å)          |
| Membrane glycoprotein polyprotein and beta-sesquiphellandrene (MPp-bS) | $-250$    | $-9.5$                    | Asp168 (2.8 Å) Ser169 (2.3 Å) Lys170 (2.5 Å)          |

![Fig. 5](image-url) Trajectory analysis for docked complexes. **a** RMSD plot (1 to 3 Å). **b** RMSF plot (1 to 8 Å)
anti-inflammatory properties especially against SARS-CoV2 [1] and alpha-herpesvirus-1 [2]. Photochemical and antioxidants from Zingiber officinalis are also effective against multiple ailments associated with various organ systems of the human body [41]. Murugesan et al. [42] recently revealed anti-arthritic role of Zingiber officinalis. Molecular docking and simulation studies provide major evaluation basis for computer-based drug discovery studies [43]. Our study reveals the importance of one of the ginger compound beta-sesquiphellandrene affecting viral entry for both SARS-CoV2 and SFTS viruses which act as lifesaving in this pandemic time.

Conclusion
Ginger, a traditional medicinal food item, contains beta-sesquiphellandrene that has potential therapeutic properties. Our study reveals that this molecule interacts and binds to spike protein of SARS-CoV2 and membrane glycoprotein polyprotein of SFTS virus to inhibit their further interaction to cells. The method of computational analysis was found to be rapid and effective and opens new doors in the domain of computational drug discovery. Beta-sesquiphellandrene can be used as effective medicine to control these harmful pathogens after wet lab validations.

Abbreviations
SARS-CoV2: Severe acute respiratory syndrome coronavirus 2; SFTS Virus: Severe fever with thrombocytopenia virus; RMSD: Root mean square deviation; RMSF: Root mean square fluctuation; ACE value: Atomic contact energy value; ACE receptor: Angiotensin-converting enzyme; Sp: Spike protein; MPp: Membrane glycoprotein polyprotein; bS: Beta-sesquiphellandrene; MD: Molecular dynamics

Acknowledgements
All the authors are thankful towards School of Bioengineering and Biosciences, Lovely Professional University, Phagwara, Punjab (India).

Authors’ contributions
AJ and SKG conducted this research study, VK guided AJ and SKG in designing and resolving the research problem. All authors have read and approved the manuscript.

Funding
Not applicable

Availability of data and materials
All data is provided in the manuscript.

Ethics approval and consent to participate
Not applicable. No impact on ethical standards in this study and there is no human or animal involvement.

Consent for publication
Not applicable.

Competing interests
All authors have no conflict of (competing) interests.

Received: 17 August 2020 Accepted: 16 November 2020
Published online: 27 November 2020

References
1. Asif, M., Saleem, M., Saadullah, M., Yaseen, H. S., & Ali Zarzour, R. (2020). COVID-19 and therapy with essential oils having antiviral, anti-inflammatory, and immunomodulatory properties. Inflammopharmacology, 28(5), 1153–61. https://doi.org/10.1007/s10787-020-00744-0
2. Camero M, Lanave G, Catella C, Capozza P, Gentile A, Fracchiolla G et al (2019) Virucidal activity of ginger essential oil against caprine alphaherpesvirus-1. Vet Microbiol 230:150–155
3. Denyer CV, Jackson P, Loakes DM, Ellis MR, Young DA (1994) Isolation of antirhinoviral sesquiterpenes from ginger (Zingiber officinale). J Nat Prod 57(5):658–662
4. Crichton M, Marshall S, Marx W, McCarthy AL, Isenring E (2019) Efficacy of ginger (Zingiber officinale) in ameliorating chemotherapy-induced nausea and vomiting and chemotherapy-related outcomes: a systematic review update and meta-analysis. J Acad Nutr Diet 119(12):2055–2068
5. Pongseenuyakarn T, Vyanant V, Euristitchichai V, Tesana S, Chaiaเราenkul W, Itharat A, Na-Bangchang K (2012) Cytotoxicity, toxicity, and anticancer activity of Zingiber officinale Roscoe against cholangiocarcinoma. Asian Pac J Cancer Prev 13(9):4597–4606
6. Yeh HY, Chiang CH, Chen HC, Wan CJ, Chen TL, Lin LY (2014) Bioactive components analysis of two various gingers (Zingiber officinale Roscoe) and antioxidant effect of ginger extracts. LWT-Food Science and Technology 55(1):329–334
7. Singh, J. (2013). Manufacturing Jaggery, a Product of Sugarcane, As Health Food. Agrotechnology, 01(511). https://doi.org/10.4172/2168-9881.11-007.
8. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X et al (2020) Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci 63(3):457–460
9. Tari H, Kawachi K, Kimura M, Taniguchi S, Shimjojima M, Fukushima S et al (2019) Identification of the amino acid residue important for fusion of severe fever with thrombocytopenia syndrome virus glycoprotein. Virology 535:102–110
10. Joshi A, Joshi BC, Mannan, M. A., & Kaushik, V. (2020). Epitope based vaccine prediction for SARS-CoV-2 by deploying immunoinformatics approach. Informatics in Medicine Unlocked, 19, 100338. https://doi.org/10.2174/1871526520666200921154149.
11. Joshi A, Joshi BC, Mannan, M. A., & Kaushik, V. (2020). Epitope based vaccine prediction for SARS-CoV-2 by deploying immunoinformatics approach. Informatics in Medicine Unlocked, 19, 100338. https://doi.org/10.2174/1871526520666200921154149.
12. Spiegel M, Plegge T, Pöhlmann S (2016) The role of phlebovirus host factor for SFTS virus infection by CRISPR knockout screening. Virol Sin 31:539–546
13. Ortiz-Prado E, Simbaña-Rivera K, Gómez-Barreno L, Rubio-Neira M, Guaman LP, Kyriakidis NC, López-Cortés A (2020). Clinical, molecular, and epidemiological characterization of the SARS-CoV-2 virus and the Coronavirus Disease 2019 (COVID-19), a comprehensive literature review. Diagn Microbiol Infect Dis 2019:1–6. https://doi.org/10.1016/j.diagmicrobio.2020.115094.
14. Zhao J, Cui W, Tian BP (2020) The potential intermediate hosts for SARS-CoV-2. Front Microbiol 11. https://doi.org/10.3389/fmicb.2020.580137
15. Äkhtar N, Joshi A, Singh B, Kaushik V (2020) Immunoinformatics quest against COVID-19/SARS-CoV-2: determining putative T-cell epitopes for vaccine prediction. Infect Disorders Drug Targets. https://doi.org/10.2174/1871526520666200921154149.
16. Singla R, Mishra A, Joshi R, Jha S, Sharma AR, Upadhyay S et al (2020) Human animal interface of SARS-CoV-2 (COVID-19) transmission: a critical appraisal of scientific evidence. Vet Res Commun 1–12. https://doi.org/10.1007/s11259-020-09781-0.
17. Ortiz-Piado E, Simbaña-Rivera K, Gómez-Barreno L, Rubio-Neira M, Guaman LP, Kyriakidis NC, López-Cortés A (2020). Clinical, molecular, and epidemiological characterization of the SARS-CoV-2 virus and the Coronavirus Disease 2019 (COVID-19), a comprehensive literature review. Diagn Microbiol Infect Disease, 98(1), 115094. https://doi.org/10.1016/j.diagmicrobio.2020.115094.
18. Jin C, Jiang H, Liang M, Han Y, Gu W, Zhang F et al (2015) SFTS virus infection in nonhuman primates. J Infect Dis 211(6):915–925
19. Yamaoka, S., Weisend, C., & Ebihara H. (2020). Identifying target cells for a tick-borne virus that causes fatal hemorrhagic fever. Journal of ClinicalInvestigation, 130(2), 588–600. https://doi.org/10.1172/jci134512.
20. Fisher D, Heymann D (2020) Q&A: the novel coronavirus outbreak causing COVID-19. BMC Med 18(1):1–3
21. Jin C, Liang M, Ning J, Gu W, Jiang H, Wu W et al (2012) Pathogenesis of emerging severe fever with thrombocytopenia syndrome virus in CS7BL/6 mouse model. Proc Natl Acad Sci 109(25):10033–10038

22. Funk CD, Laferrère C, Ardanaki A (2020) A snapshot of the global race for vaccines targeting SARS-CoV-2 and the COVID-19 pandemic. Front Pharmacol 11:937

23. Suzuki T, Sato Y, Sano K, Arashiro T, Katano H, Nakajima N, ... Hasegawa H (2020). Severe fever with thrombocytopenia syndrome virus targets B cells in lethal human infections. Journal of Clinical Investigation, 130(2),799–812. https://doi.org/10.1172/jci129171.

24. Daina A, Michellin O, Zoete V (2017) SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 7:42717.

25. Lipinski CA (2004) Lead- and drug-like compounds: the rule-of-five revolution. Drug Discov Today Technol 1(4):337–341

26. O’Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Huchison GR (2011) Open Babel: an open chemical toolbox. J Cheminformatics 3(1):33

27. Schneidman-Duhovny D, Inbar Y, Nussinov R, Wolfson HJ (2005) PatchDock and SymmDock: servers for rigid and symmetric docking. Nucleic Acids Res 33(suppl_2):W363–W367

28. DeLano WL (2002) PyMOL: an open-source molecular graphics tool. CCP4 Newsletter on protein crystallography 40(1):82–92

29. Trott O, Olson AJ (2010) AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem 31(2):455–461

30. Van Der Spoel D, Lindahl E, Hess B, Groenhof G, Mark AE, Berendsen HJ (2005) GROMACS: fast, flexible, and free. J Comput Chem 26(16):1701–1718

31. Hussain ME, Hoque MA, Alam MB, Yusuf MA, Chowdhury RN, Mohammad QQ (2020) Neurological manifestations of COVID-19 patients: an updated review and observations of COVID patients in the National Institute of Neurosciences and Hospital, Dhaka, Bangladesh. J Bangladesh Coll Physicians Surg 12:1–12.

32. Matsuno K, Orba Y, Naide-White K, Scott D, Feldmann F, Liang M, Ebihara H (2017) Animal models of emerging tick-borne phleboviruses: determining target cells in a lethal model of SFTSV infection. Front Microbiol 8:104

33. Ohagi Y, Tamura S, Nakamoto C, Nakamot H, Saito M, Shimojima M, ... Fujimoto T (2014). Mild Clinical Course of Severe Fever with Thrombocytopenia Syndrome Virus Infection in an Elderly Japanese Patient. Case Reports in Infectious Diseases, 2014, 1(1080/07391102.2020.1752802.

34. Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J et al (2020) Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med 26(8):1200–1204

35. GSK, Joshi A, Kaushik V (2020) T cell epitope designing for dengue peptide vaccine using docking and molecular simulation studies. Mol Simul 46(10):787–795. https://doi.org/10.1016/j.molsim.2020.07.0722022.2020.1772970

36. Sharma P, Kaur R, Upadhyay AK, Kaushik V (2020) In silico prediction of peptide based vaccine against Zika virus. Int J Pept Res Ther 26(1):85–91

37. Joshi A, Kaushik V (2020) In-silico proteomic exploratory quest: crafting T-cell epitope vaccine against Whipple disease. Int J Pept Res Ther 1:1 https://doi.org/10.1016/j.ijpt.2020.100345.

38. Elfiky AA. (2020). Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. Life Sciences, 253, 117592. https://doi.org/10.1016/j.lfs.2020.117592.

39. Muralidharan N, Sakthivel R, Velmurugan D, & Gromiha MM. (2020). Computational studies of drug repurposing and synergism of lopinavir, oseltamivir and ritonavir binding with SARS-CoV-2 protease against COVID-19. Journal of Biomolecular Structure and Dynamics, 1–13. https://doi.org/10.1080/08927022.2020.1775202.

40. Tsuda Y, Igarashi M, Ito R, Nishio S, Shimizu K, Yoshimatsu K, Arikawa J (2017) The amino acid at position 624 in the glycoprotein of SFTSV (severe fever with thrombocytopenia virus) plays a critical role in low-pH-dependent cell fusion activity. Biomed Res 38(2):89–97

41. Zeeshan U, Barkat MQ, Mahmood HK (2018) Phytochemical and antioxidant screening of Cassia angustifolia, Curcuma zedoaria, Embelia ribes, Piper nigrum, Rosa damascena, Terminalia belerica, Terminalia chebula, Zingiber officinale and their effect on stomach and liver. Matrix Sci Pharma 2(2015–2016):787–795.

42. Murugesan S, Venkateswaran MR, Jayabal S, Periyasamy S (2020) Evaluation of the antioxidant and anti-arthritis potential of Zingiber officinale Rosc. by in vitro and in silico analysis. S Afr J Bot 130:45–53

43. Peele KA, Potia Durthi C, Srisans A, Krupanidhi S, Ayagari VS, Babu DJ, Venkateswaralu TC. (2020). Molecular docking and dynamic simulations for antiviral compounds against SARS-CoV-2: A computational study. Informatics in Medicine Unlocked, 15, 100345. https://doi.org/10.1016/j.imu.2020.100345.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.