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MINI REVIEW

Predictive analysis, diagnosis of COVID-19 through computational screening and validation with spectro photometrical approach

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Abstract

Objective To develop Favipiravir, based predictive models of coronavirus disease 2019 (COVID-19) from small molecule databases such as PubChem, Drug Bank, Zinc Database, and literature.

Methods High Throughput Virtual Screening (HTVS) using different computational screening methods is used to identify the target and lead molecules. CoMFA (Comparative Molecular Field Analysis) is a 3D-QSAR procedure depending on information from known dynamic atoms and eventually permits one to plan and anticipate exercises of particles. These two analysis is used to train predictive models.

Results The predictive model achieved the highest accuracy score with a relatively small dataset size can be a subject of overfitting. Datasets with over 500 samples demonstrate an accuracy of about 85–95%, that can be considered as very good.

Conclusions From the result it is observed that Increasing level of potassium, sodium and nitrogen will lead to burst lipid bilayer membrane of virus which cause RNA replication rapidly. However, low level of sodium, potassium and nitrogen will help in the DNA polymerase inhibition and replication can be stopped. The best developed QSAR model in terms of the druggability and activity relation has been selected over the parent Favipiravir molecule for designing COVID-19 drugs may lead towards pharmaceutical development in future.

Keywords Favipiravir · COVID-19 · Structure-based drug design · Virtual screening

Abbreviations

COVID-19	Corona Virus Disease 2019
2019-nCoV	2019 Novel coronavirus
RdRp	RNA dependent RNA polymerase
HTVS	High throughput virtual screening
NCP	Nursing care plan
NMDA	National Medical Products Administration
T-705RTP	Ibofuranosyl-5′-triphosphate
RNA	Ribonucleic acid
SARS-CoV	Severe acute respiratory syndrome coronavirus
MERS-CoV	Middle East respiratory syndrome coronavirus
ADMET	Absorption, distribution, metabolism, excretion, and toxicity
QSAR	Quantitative structure–activity relationship
3D-QSAR	3 Dimensional quantitative structure–activity relationship
CoMFA	Comparative subatomic field investigation
CoMSIA	Relative subatomic closeness records examination
SARS	Severe acute respiratory syndrome
ICMR	Indian Council of Medical Research
CFR	Case fatality rate
MERS	Middle East respiratory syndrome
WHO	World Health Organization
mRNA	Messenger RNA
HIV	Human immunodeficiency virus
3CLpro	3-Chymotrypsin-like protease
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

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SARS-CoV-1	Severe acute respiratory syndrome coronavirus 1
FDA	Food and Drug Administration
DNA	Deoxyribonucleic acid
MM/GBSA	Molecular mechanics with generalized born and surface area solvation
eMBrAcE	Multi-Ligand Bimolecular Association with Energetic
3D	3 Dimensional

Introduction

An episode of 2019-nCoV contamination that started in China had begun spreading to countries all over the globe [6, 17–19]. Lack of specific antiviral medications has been endorsed for treating COVID-19. Notwithstanding suggested antiviral medications such as interferon-α, lopinavir/ritonavir, ribavirin, and chloroquine phosphate, few clinical preliminaries emphasizing on infection RNA dependent RNA polymerase (RdRp) inhibitors have been enrolled and started. Favipiravir, a purine nucleic corrosive simple as well as a strong RdRp inhibitor supported which was used earlier in treating flu, is likewise thought to be in a few clinical preliminaries [21]. Be that as it may, no particular antiviral medications have been endorsed for treating COVID-2019. Interferon-α, lopinavir/ritonavir, ribavirin, chloroquine phosphate, arbidol, and blends of the above-mentioned medications, are suggested in accordance with the 7th update of the Chinese National Health Commission's Treatment Regimen. Meanwhile, alternative conceivable pressing anticipations together with treatment choices are talked about elsewhere [13, 21].

Crisis endorsement of Favipiravir for a clinical preliminary in grown-up patients with NCP (2020L00005) was likewise declared in accordance with the National Medical Products Administration (NMDA) in China. Favipiravir is a pyrazine carboxamide subsidiary (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) as well as an expansive range of antiviral medication supported in Japan for treating flu [15]. Favipiravir is favorable in medicating which is intracellularly ribosylated and phosphorylated and also in shaping favipiravir ibofuranosyl-5′-triphosphate (T-705RTP), a dynamic metabolite [15]. T-705-RTP rivals purine nucleosides as well as meddle in viral replications by joining the infected RNA and accordingly hinders the RNA dependent RNA polymerase (RdRp) of RNA infections.

The 2019-nCoV genome sequencing distinguished the infection similar to a solitary-abandoned RNA beta-Covid with the RdRp quality like those of SARS-CoV and MERS-CoV [38 (, Lu et al. 2020). Therefore, Favipiravir is regarded as an expected possibility for treating COVID-19 [2, 22]; however, affirmed in vitro and preclinical creature examines are still not accessible. A clinical preliminary assessing security as well as adequacy of Favipiravir in treating COVID-19 (ChiCTR2000029600) was directed in Shenzhen, with 80 patients enlisted [4]. Outcomes showed that thirty-five patients in the Favipiravir arm exhibited altogether more limited viral freedom time as contrasted than the forty-five patients in the control arm (middle 4 days vs. 11 days). The X-beams assessment affirmed higher pace of progress in imaging of the chest in the Favipiravir arm (91.43% vs. 62%) [4]. A multifocused randomized clinical examination (ChiCTR200030254) additionally recommended compelling control of Favipiravir on COVID-19 [7]. For normal persons infected with COVID-19, the multiday's clinical rate of recuperation expanded from 55.86 to 71.43% with Favipiravir treatment. For normal patients with COVID-19 and hypertension as well as diabetes-related complications, the hour of fever decrease and hack help in the Favipiravir treatment bunch has further diminished fundamentally [7].

At this intersection, certain current methodologies for discovering new ways for remedial targets are progressively found on 3-Dimensional data with respect to receptors. A compelling method which foresees restricting the constructing substrate in its receptor is docking reproduction, which in particular, has effectively been employed in numerous applications. Docking methodology fundamentally plans to distinguish right conformities pertaining to ligands in the limiting pocket of a protein as well as foresees ligand–protein interactions. Finally, it is anything but a cycle through which two particles hinge together into 3-Dimensional space [3]. Mixes related to the technique include different strategies, such as subatomic powerful reproduction, free-restricting energy estimation, ADMET prediction, 2D and 3D QSAR demonstrations. Comparative subatomic field investigation (CoMFA) and relative subatomic closeness records examination (CoMSIA) empower to get a ton of experiences on natural frameworks and to help reasonable medication plans for mimicking most strongest compound (Lead compound) that has drug resemblance properties [27]. None of the review paper has not consider the following points.

1. To study the mechanism of interaction of antiviral agents as a RdRP inhibitors rationally.
2. To identify efficient Favipiravir derivatives as an antiviral agent using virtual screening approach.
3. To study the prediction of pharmacokinetics properties of Favipiravir derivatives through binding affinity QSAR modeling.
4. To study the molecular dynamics and simulation of lead Favipiravir-RdRp binding domain.
5. To study the drug response by developing Spectrophotometricaldevice by sensing the level of sodium, potassium in the blood serum.

Status of research and development in COVID19

As COVID-19 is an arising infection, a compelling treatment has not been produced for illness coming in because of this infection [36–38]. Taking into account the previous proof on adequacy of lopinavir/ritonavir resistant to SARS and MERS-CoV infections as per the Indian Council of Medical Research (ICMR), an off-mark crisis utilization of lopinavir/ritonavir mix for person indicative with COVID-19 symptoms throughout the nation has been suggested. Utilization of the drugs such as IFN-β1b and ribavirin was not taken into consideration because of their revealed poisonous nature, although oseltamivir was not taken into consideration because of its problematic adequacy in fighting against CoVs [23]. The total clinical image of COVID-19 is not completely perceived. Clinical appearances in contaminated persons could go from gentle ailment to serious sickness requiring affirmation of ICU and ventilatory help. The case fatality rate (CFR) of COVID-19 is a little lower than those of SARS (CFR: 14–15%) and MERS (34%) [33, 34]. To date, no compelling treatment has been suggested for COVID-19, with the exception of fastidious strong consideration [35]. The ICMR suggested lopinavir/ritonavir mix treatment for lab-affirmed persons infected with COVID-19 depending on the basis of observational investigations of clinical advantages among persons with SARS-CoV and MERS-CoV [5, 9, 12] similar to the docking contemplates directed in accordance with the National Institute of Virology, Pune [1]. The Indian Regulatory Authority and the Central Drugs Standard Control Organization have agreed on endorsement for limited general well-being crisis utilization of this treatment protocol (Lu et al. 2017) [9]. The RdRp inhibitors which are the basics for the CoV record and replication are engaged with creating the genomic and subgenomic RNAs. Nucleoside analogs such as Favipiravir, ribavirin, penciclovir, remdesivir and galidesivir are notable RdRp inhibitors. A guanosine simple, ribavirin, showed an expansive range of antiviral actions against a few infections including respiratory syncytial infection, hepatitis C and E infections (HCV, HEV), chikungunya, and viral hemorrhagic fevers [24, 28] (Figs. 1, 2).

Despite the fact that the system of activity is not completely perceived, it is conjectured that the medication might be engaged with the restraint of mRNA covering or viral RNA amalgamation. The in vitro antiviral movement of ribavirin against SARSCoV-1 and MERS-CoV [31] and in rhesus monkeys contaminated with MERS-CoV has been observed [14]. The medication has been employed in treating persons with SARS and MERS; however, advantages are questionable. Furthermore, in seriously tainted

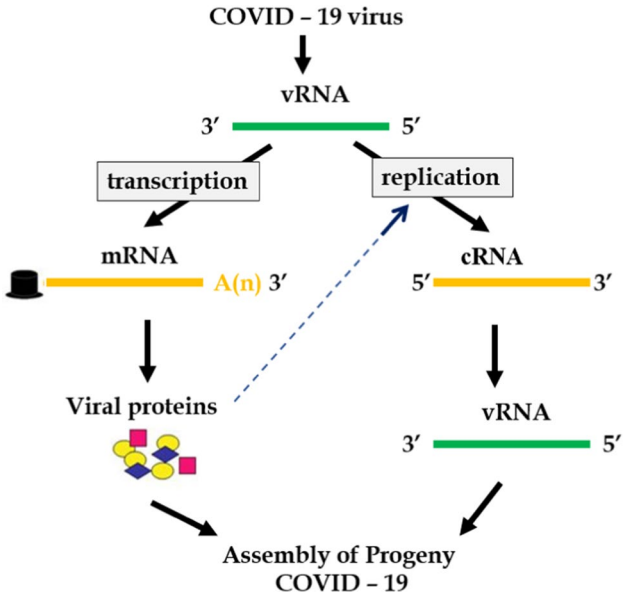

Fig. 1 Potentially inhibiting the RNA-dependent RNA polymerase (RdRp) of RNA viruses

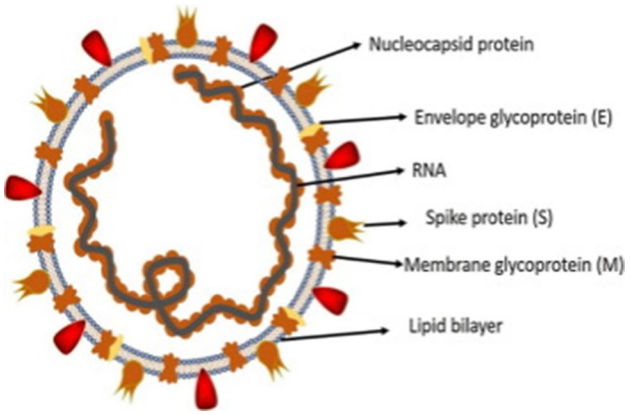

Fig. 2 Different parts of RNA virus

CoV patients, there could be results related with high dosages [14, 29, 32].

Favipiravir (EC50 = 61.88 μM, CC50 > 400 μM, SI > 6.46) is used in decreasing the viral load of the disease and has also been demonstrated to be one hundred percent powerful in securing mice against the Ebola infection challenge, despite the fact that its EC50 esteem in Vero E6 cells was extremely high as 67 μM, whereas chloroquine (EC50 = 1.13 μM; CC50 > 100 μM, SI > 88.50) strongly impeded infection contaminations at low micromolar fixation, but is highly dangerous because it can impact heartbeat [8, 25, 30].

The limiting capability of HIV-1 protease inhibitors, lopinavir, as well as ritonavir against 3CLpro of SARS-CoV-2 uses computational docking considers. The Novel COVID19

protein is shown in Fig. 3. This would help acquire a deeper understanding into the subatomic method of activity of these medications which are under clinical preliminaries against SARS-CoV-2 and further gauges near inhibitory power of the FDA-supported HIV protease inhibitors to the SARS-CoV-2 [1, 5, 12].

Importance of the proposed approach

Antiviral agents used in the prophylaxis or treatment of infection sicknesses: a portion of the manners in which they may act incorporate forestalling viral replication by hindering viral DNA polymerase; restricting to explicit cell-surface receptors and restraining viral entrance or uncoating; repressing viral protein combination; or impeding late phases of infection get together [11, 15, 26, 32]. Favipiravir is a pyrazinecarboxamide subordinate with movement against RNA infections. Favipiravir is changed over to the ribofuranosyltriphosphate subordinate through chemicals and specifically hinders the flu viral RNA-subordinate RNA polymerase. Favipiravir varies from the presently supported enemy of flu drugs in which it targets the flu viral polymerase. It has been recommended that cell proteins (cell kinases) convert Favipiravir into a Favipiravir ribofuranosyl phosphate, a structure that represses infection polymerase without influencing host cell RNA or DNA combination [8, 20, 30].

In view of existing writing and lacunae, the accompanying system is recommended.

6. Study the mechanisms of interactions of antiviral agents as RdRP inhibitors rationally.
7. Identify efficient Favipiravir subsidiaries as an antiviral agent using the virtual screening approach.
8. Study the prediction of pharmacokinetic properties of Favipiravir derivatives through binding affinity QSAR modeling.
9. Study the molecular dynamics and simulation of lead Favipiravir-RdRp-binding domain.
10. Study the drug response by developing a spectro-photometrical device by sensing the level of sodium and potassium in the blood serum.

Methodology

Preparation of compound libraries

A compound library of Favipiravir comprising analogs will be arranged depending on the parental construction as a format using the combinatorial science plan. These analogs will be developed by the underlying change of the ring structure

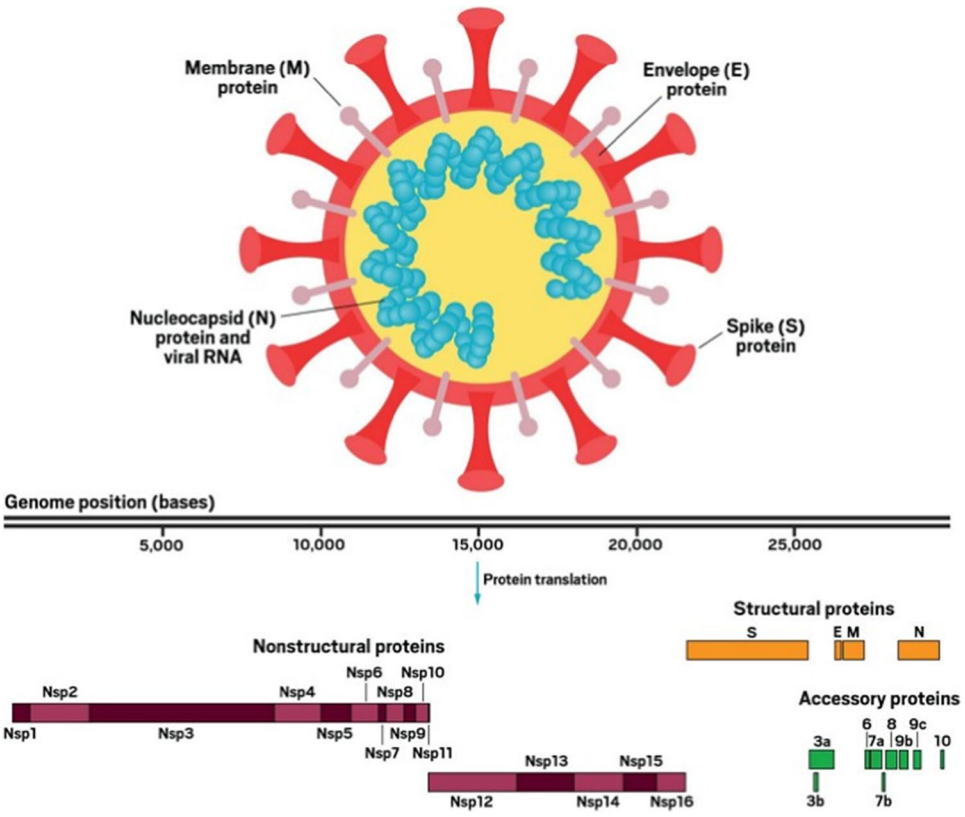

Fig. 3 Novel COVID-19 proteins

with sterically as well as conformationally permitted substituent making use of the reagent information base and combinatorial plan module (Schrödinger).

Computational screening based on docking and scoring function

The scoring capacity used by docking techniques to position the particles depending on their partiality of cooperation will be valuable to screen out the better analogs from the library.

Computational screening based on MM/GBSA and free energy of binding

Blends related to docking technique include different strategies, such as MD reproduction and free energy restricting computation, empower to get a ton of experiences on organic frameworks and to help reasonable medication plans. Subatomic elements are a type of PC reproduction where iotas and particles are permitted to collaborate for a while under known laws of material science. By and large starts where exploratory design assurance leaves off, if not during the construction refinement itself. The reproduction can crease stretched out successions to "worldwide" potential energy minima for little frameworks (peptides of length ten or thereabouts, in vacuum); however, it is most ordinarily used to recreate the elements of known designs. A few different ways to compute free energy of restricting have been recommended and used in various applications [11, 15, 25, 32]. To contemplate the relationship of the ligands with the receptor, we will use the robotized instrument of Multi-Ligand Bimolecular Association with Energetic (eMBrAcE). It uses customary MM strategies in figuring out ligand-receptor collaboration energies, with a Gaussian Smooth Dielectric Constant capacity strategy for an electrostatic piece of solvable energy and a dissolvable open surface for the nonpolar piece of solvable energy [26].

ADME prediction and modeling for screening of analogues

Acknowledgment by the drug business that bothersome retention, appropriation, digestion, and discharge properties of new medication up-and-comers are the reasons for some disappointments during clinical-stage drug improvements. This has brought about a change in perspective to distinguish such issues right off the bat in the medication disclosure measure. In this way, presently, in vitro approaches are broadly used in examining the Absorption, Distribution, Metabolism, and Excretion (ADME) properties of new synthetic substances as well as, all the more as of late, computational (in silico) demonstrating has been researched as a device in upgrading choice of the most reasonable contender for improvement of drugs. QikProp is a speedy, precise, simple to use the ADME program planned by Professor William L. Jorgensen. It will assist us with anticipating truly critical descriptors and chemically applicable properties of Favipiravir and its analogs (Holshue,et al. 2020).

Computational screening based on 3D QSAR (COMFA/COMSIA)

CoMFA (Comparative Molecular Field Analysis) is a 3D-QSAR procedure depending on information from known dynamic atoms and eventually permits one to plan and anticipate exercises of particles. The point of CoMFA study will be to infer a connection between the organic movement of a bunch of particles and its 3D shape, electrostatic, and hydrogen-holding qualities. This relationship will be gotten from a progression of superimposed adaptations, one for every particle in the set. These compliances are dared to be the organically dynamic designs, overlaid in their normal restricting mode. Every compliance is taken, and thus the atomic fields around it are determined.

Spectrophotometer

A spectrophotometer is an optical gadget that can decide the grouping of a compound or particle in an answer or suspension. The example blood serum, sodium, for instance, will ingest a portion of the light. The measure of light that is consumed increases with expanding quantities of microbes in an anticipated manner.

The spectrophotometer strategy measures light power as an element of wavelength. This is done by diffraction of the light bar into a range of frequencies, distinguishing the powers using a charge-coupled gadget, as well as showing the outcomes through a diagram on the identifier and the presentation gadget afterward.

Figure 4 shows working principle of a spectrophotometer and Fig. 5 display the typical layout of a spectrometer.

The spectrometer range delivered by the grinding process is projected onto a diagram paper in order to create a size of frequency. The grinding might pivot or cut, and the test might move to choose various frequencies of light.

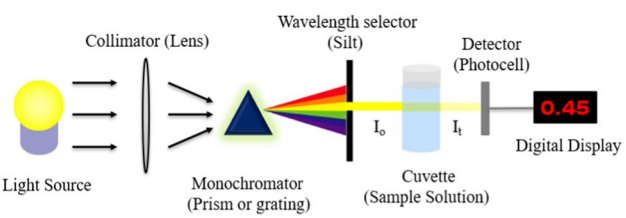

Fig. 4 Working principle of a spectrophotometer

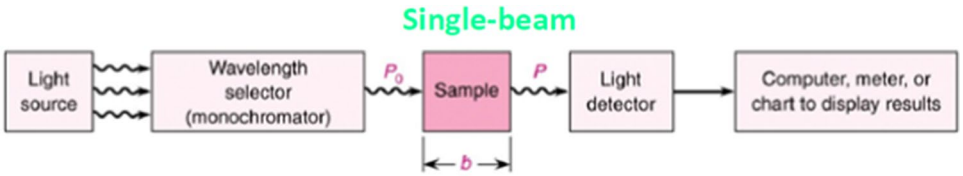

Fig. 5 A typical layout of a spectrophotometer

Table 1 Typical perceived colors and wavelengths of visible light

S. no.	Color	Wavelength center/nm	Wavelength range/nm
1	Violet	410	400–430
2	Blue	470	430–490
3	Green	520	490–570
4	Yellow	580	570–595
5	Orange	610	595–650
6	Red	650	650–700

Alignment of the frequency is carried out using a high goal camera, by making use of the numbers in Table 1 as an aid. In order to develop a range, absorbance should be determined for every frequency, as well as in the way as follows: Vzero, Vwater, and Vsample. All the 3 parameters should be estimated at each point. Experimental set up for signal capturing and processing is shown in Fig. 6.

Table 1 displays the typical perceived colors and wavelengths of visible light (The perceived colors vary between individuals, especially at the boundary wavelengths). Ambient light when comes in contact with the spectrophotometer brings about inaccuracies and hence hugecardboard boxes or thick blackout curtains draped between two and three retort stands are used to keep out light. The second-mentioned is ideal because students will be able to work under the material. No specific method to assemble a spectrophotometer has been designed, and it is found that students often devise ideas that have not been thought of so far. A simple instrument can be created by the use of colored filters in the location of the grating–lens–slit assembly, although the number of data points is constrained to the number of available filter colors.

Working of a spectrophotometer

- The white light source is allowed to pass through a monochromator (a prism or diffraction grating which diffracts the white light into all colors of the visible spectrum).

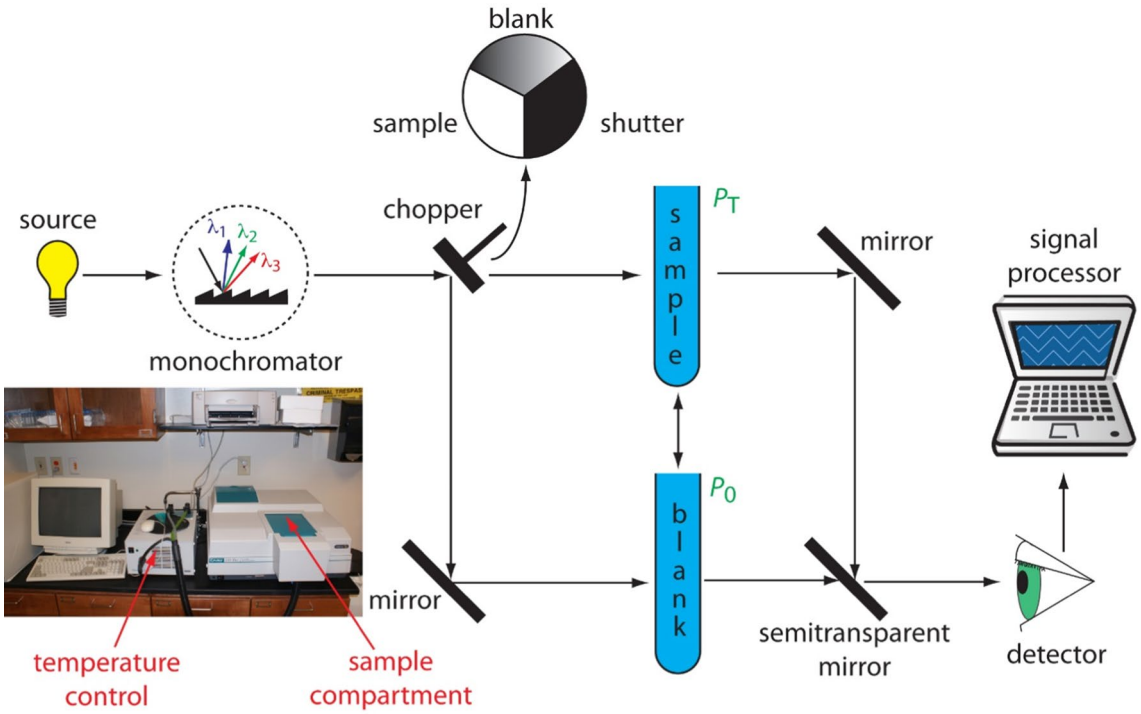

Fig. 6 Test set up IR spectroscopy

- Once the light is separated, it then travels through a filter (to block out unwanted light, sometimes light of a different color) and a slit (to narrow down the beam of light).
- Next, the beam of light penetrates the sample placed over the sample holder (curette).
- The light permeates the sample, and the unabsorbed portion (reflected) strikes the photodetector and an electrical signal is generated. The electrical signal produced by the photodetector is proportional to the intensity of light.
- The signal is then converted to a readable output(absorbance), and it is used for the sample analysis.
- The calibration curve is later generated by measuring the absorbance of several solutions which contain known concentrations of the analytic.

Measuring the absorbance

1. Preheating
2. Set Wavelength
3. Adjust 0% (T) and 100% (T)
4. Switch to absorbance Mode
5. Set sample for measuring
6. Read data

In the calibration curve, the level of sodium, potassium, and nitrate presence in the blood sample is observed. An all-in-one sensor for nitrogen, phosphorus, and potassium assessment developed through an online system for integration is an ideal device in enabling more sustainability for treatment. Nevertheless, present knowledge and technology have neither developed a portable, integral sensor to measure the aforementioned three key parameters in the blood sample by means of a simple, straightforward, and cost-effective way to maintain the accuracy of standard methodologies. Therefore, a compact benchtop system is proposed with a D2 (deuterium) light source (Ocean Optics model DH-2000-BAL). In addition, the integrated system includes a spectrometer (Ocean Optics model HR4000), a transmission optical fiber bundle, as well as a stainless steel slitted reflection probe for the process of insertion on samples and/or sampling chambers [10].

Relevance of sodium and potassium in the study in the detailed project has been incorporated as follows:

Favipiravir (T-705-RTP) competes with purine nucleosides and interferes with viral replication by incorporating them into the virus RNA, and thus potentially inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses. Increasing the level of potassium, sodium, and nitrogen will lead to bursting of the lipid bilayer membrane of the virus which causes RNA replication rapidly. However, low levels of sodium, potassium, and nitrogen will help in the DNA polymerase inhibition and replication can be stopped. A spectrophotometrical device will sense potassium, sodium, and nitrogen levels after introducing the drug into the animal.

Discussion

Environmental impact assessment and risk analysis

These kinds of rapid tests are quick to create as well as user-friendly. However, they have to be carefully designed and validated; hence, they are not being approved for use, and we have not seen their widespread official use yet. Quality control and validation are two factors that add significant cost to these tests. Many may duplicate the model and misuse it.

It is devastating to note the inaccuracy of these tests in the current outbreak–for example, if a person gets tested negative, but was affected, he/she tends to go out and spread the infection to many people. Few of these tests have an accuracy rate of around 80%–this has been studied intensively for many important viral infections such as dengue–which sounds great, except one in five test results goes wrong.

Variations in errors occur owing to the ailment. For certain infections, tests give a positive result if the person had by-no-means contracted the coronavirus, as he/she might have antibodies against something similar. For the majority of these rapid tests, a negative result could be read as the line in the device would be too hard to notice.

Combinations of the docking method with other methods, such as MD simulation, free energy binding calculation, enable to get a lot of insights on biological systems and to help rational drug design. Molecular dynamics (MD) is a form of computer simulation where atoms and molecules are allowed to interact for a period of time under known laws of physics. It generally begins where experimental structure determination leaves off, if not during the structure refinement itself. The simulation can fold extended sequences to `global' potential energy minima for very small systems (peptides of length ten, or so, in vacuum), but it is most commonly used to simulate the dynamics of known structures. Several ways to calculate free energy of binding (FEB) have been suggested and used in different applications. The most effective prediction models were based on using Random forest, Gradient boosting, and their variations. The predictive model achieved the highest accuracy score with a relatively small dataset size can be a subject of overfitting. Datasets with over 500 samples demonstrate an accuracy of about 85–95%, that can be considered as very good.

Conclusion

The current work initiates with the compilation of a virtual library of pyrzinecarboxymide derivative analogues collected from chemical library. The set of derivatives were

then predicted for the Favipiravir properties and found to have satisfying druggability from the obtained values.

Different computational screening methods, such as Structure-Based Drug Design (SBDD) like docking and simulation, scoring and rescoring function and Ligand-Based Drug Design (LBDD) like 2D, 3D and Pharmacophore-based QSAR (CoMFA & CoMSIA) is identified the target and lead molecule.

The results would help gain an in-depth understanding of the relative binding affinity and design of derivatives with greater binding potential at the enzyme active site. To validate the Computer Aided Drug Design (CADD) outcome, a device is developed to understand the drug response with the help of spectrophotometrical approach by sensing the level of sodium, potassium and nitrogen in the blood serum into the target site in terms of Pharmacodynamics and Pharmacokinetics after importing the lead compound from chemical vendors by incorporating the same to the animal. From the result it is observed that increasing level of potassium, sodium and nitrogen will lead to burst lipid bilayer membrane of virus which cause RNA replication rapidly. However, low level of sodium, potassium and nitrogen will help in the DNA polymerase inhibition and replication can be stopped.

The best developed QSAR model in terms of the drug ability and activity relation has been selected over the parent Favipiravir molecule for designing COVID-19 drugs may lead toward pharmaceutical development in future.

A combined approach of computational screening methods adopted in this proposal of the analogs designed for Favipiravir will provide an insight into effective antiviral agents against RdRp. In addition, development of the docking simulation, ADMET profiling, and QSAR modeling, and simulation for computational screening, including pharmacokinetic and pharmacodynamic profiling of Favipiravir analogs provided a unique platform to all the researchers working in this field to identify and optimize the lead Favipiravir compound having maximum activity and less toxicity against the target. After the simulation test, it is identified that Favipiravir compound is the most suitable for diagnosis of COVID19. The most suitable compound (Lead compound) can be imported from the chemical vendors, and the same compound is introduced into the animal and tested based on the animal ethical committee approval by using a developed spectrophotometrical device. Once the drug starts responding well, the simulated structure of the drug will be the subject for further clinical and post-clinical research followed by manufacture.

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Declarations

Conflict of interest Authors declare that they have no conficts of interest.

Compliance with ethical standards This article does not contain any studies with animals performed by any of the authors.

References

1. Anon (2020) Coronavirus disease (COVID-19) in neonates: current perspectives. J Pediatr Neonatal Biol https://doi.org/10.33140/jpnb.05.04.04.
2. Ashok G, John IBP, Mary T, Packiavathy SV, Gautam S (2023) Internet of Things (IoT) based automated sanitizer dispenser and COVID-19 statistics reporter in a post-pandemic world. Heal Technol. https://doi.org/10.1007/s12553-023-00728-4
3. Bai CQ, Mu JS, Kargbo D, Song YB, Niu WK, Nie WM, Kanu A, Liu WW, Wang YP, Dafae F, Yan T (2016) Clinical and virological characteristics of Ebola virus disease patients treated with favipiravir (T-705)—Sierra Leone, 2014. Clin Infect Dis 63(10):1288–1294
4. Basu A, Chakraborty S (2020) Faculty opinions recommendation of experimental treatment with favipiravir for COVID-19: an open-label control study. faculty opinions—post-publication peer review of the biomedical literature
5. Chan JF-W, Chan K-H, Kao RY-T, To KK-W, Zheng B-J, Li IW-S et al (2015) Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. J Infect Dis 212(12):1904–1913. https://doi.org/10.1093/infdis/jiv392
6. Changotra R, Rajput H, Rajput P, Gautam S, Arora AS (2020) Largest democracy in the world crippled by COVID-19: current perspective and experience from India. Environ Dev Sustain. https://doi.org/10.1007/s10668-020-00963-z
7. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, Chen B, Lu M, Luo Y, Zhang J, Yin P (2020) Favipiravir versus arbidol for COVID-19: a randomized clinical trial. MedRxiv
8. Chu CM, Cheng VCC, Hung IFN, Wong MML, Chan KH, Chan KS, Kao RYT, Poon LLM, Wong CLP, Guan Y, Peiris JSM (2004) Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 59(3):252–256
9. Chu CM (2004) Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 59(3):252–256. https://doi.org/10.1136/thorax.2003.012658
10. Coleman CM, Sisk JM, Mingo RM, Nelson EA, White JM, Frieman MB (2016) Abelson kinase inhibitors are potent inhibitors of severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus fusion. J Virol 90(19):8924–8933
11. Delang L, Abdelnabi R, Neyts J (2018) Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. Antiviral Res 153:85–94
12. De Wilde AH, Raj VS, Oudshoorn D, Bestebroer TM, van Nieuwkoop S, Limpens RW, Posthuma CC, van der Meer Y, Bárcena M, Haagmans BL, Snijder EJ (2013) MERS-coronavirus replication induces severe in vitro cytopathology and is strongly inhibited by cyclosporin A or interferon-α treatment. J Gen Virol 94(8):1749–1760. https://doi.org/10.1099/vir.0.052910-0
13. Dong L, Hu S, Gao J (2020) Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Therap 14(1):58–60
14. Falzarano D, De Wit E, Rasmussen AL, Feldmann F, Okumura A, Scott DP, Brining D, Bushmaker T, Martellaro C, Baseler L, Benecke AG (2013) Treatment with interferon-α2b and ribavirin

improves outcome in MERS-CoV–infected rhesus macaques. Nat Med 19(10):1313–1317
15. Furuta Y, Komeno T, Nakamura T (2017) Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B 93(7):449–463
16. Furuta Y, Takahashi K, Kuno-Maekawa M, Sangawa H, Uehara S, Kozaki K, Nomura N, Egawa H, Shiraki K (2005) Mechanism of action of T-705 against influenza virus. Antimicrob Agents Chemother 49(3):981–986
17. Gautam S, Gollakota ARK (2022) Introduction to the special issue ''Environmental impacts of COVID-19 pandemic". Gondwana Res. https://doi.org/10.1016/j.gr.2022.10.021
18. Gautam S (2020) The influence of COVID—19 on air quality in India: a boon or inutile. Bull Environ Contam Toxicol 104(6):724–726
19. Gautam S (2020) COVID—19: air pollution remains low as people stay at home. Air Qual Atmos Health. https://doi.org/10.1007/s11869-020-00842-6
20. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural A, Diaz G (2020) First case of 2019 novel coronavirus in the United States. N Engl J Med
21. Morse JS, Lalonde T, Xu S, Liu WR (2020). Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV
22. Li G, De Clercq E (2020) Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov 19(3):149–150
23. Murhekar M, Bhatnagar T, Kumar MS, Battle KE, Rade K, Saravanakumar V, ... Gangakhedkar RR (2020) Lopinavir/ritonavir combination therapy amongst symptomatic coronavirus disease 2019 patients in India: protocol for restricted public health emergency use. Indian J Med Res
24. Omrani AS, Saad MM, Baig K, Bahloul A, Abdul-Matin M, Alaidaroos AY, Almakhlafi GA, Albarrak MM, Memish ZA, Albarrak AM (2014) Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. Lancet Infect Dis 14(11):1090–1095
25. Savarino A, Di Trani L, Donatelli I, Cauda R, Cassone A (2006) New insights into the antiviral effects of chloroquine. Lancet Infect Dis 6(2):67–69
26. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, Montgomery SA, Hogg A, Babusis D, Clarke MO, Spahn JE (2020) Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 11(1):1–14
27. Sissoko D, Laouenan C, Folkesson E, M'Lebing AB, Beavogui AH, Baize S, Camara AM, Maes P, Shepherd S, Danel C, Carazo S (2016) Correction: experimental treatment with favipiravir for Ebola virus disease (the JIKI Trial): a historically controlled, single-arm proof-of-concept trial in Guinea. PLoS Med 13(4):e1002009
28. So LK, Lau AC, Yam LY, Cheung TM, Poon E, Yung RW, Yuen KY (2003) Development of a standard treatment protocol for severe acute respiratory syndrome. Lancet 361(9369):1615–1617
29. Stockman LJ, Bellamy R, Garner P (2006) SARS: systematic review of treatment effects. PLoS Med 3(9):e343
30. Su B, Wang Y, Zhou R, Jiang T, Zhang H, Li Z, Liu A, Shao Y, Hua W, Zhang T, Wu H (2019) Efficacy and tolerability of lopinavir/ritonavir-and efavirenz-based initial antiretroviral therapy in HIV-1-infected patients in a tertiary care hospital in Beijing, China. Front Pharmacol 10:1472
31. Tan EL, Ooi EE, Lin CY, Tan HC, Ling AE, Lim B, Stanton LW (2004) Inhibition of SARS coronavirus infection in vitro with clinically approved antiviral drugs. Emerg Infect Dis 10(4):581
32. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G (2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 30(3):269–271
33. World Health Organization (2003) Consensus document on the epidemiology of severe acute respiratory syndrome (SARS) (No. WHO/CDS/CSR/GAR/2003.11). World Health Organization
34. World Health Organization (2019) Middle East respiratory syndrome coronavirus (MERS-CoV)
35. World Health Organization (2020) Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance, 25 January 2020 (No. WHO/nCoV/Clinical/2020.2). World Health Organization
36. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, ... Shi ZL (2020) Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin
37. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Shi ZL (2020) Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395(10224):565–574
38. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P (2020) A novel coronavirus from patients with pneumonia in China, 2019. New Engl J Med