Phylogenetic analysis and *In silico* Screening of drug targets for ACE2 in Human and Spike Glycoprotein in Sars-CoV-2 for control of COVID19

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Research Article

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Abstract

Coronaviruses are the large group of infectious viruses that affect the respiratory tract and damages lungs. Large part to early Chinese efforts to genome sequencing of Sars-CoV-2, the virus that causes the Covid-19 disease, shared in early January 2020. The sequences from Wuhan seafood market pneumonia virus had different point mutations and are showing non-conserved patterns in between sequences from different regions of world. The present experimentation has shown that bioactive compounds like Nimbin present in Neem plant and Amlaic acid present in Amla are shown as best in the control COVID19. The bioactive compounds like Vitexin present in Bermuda grass and Curcumin present in turmeric powder were also shown good results. Hence usage of Neem, Amla, Bermuda grass and turmeric can boosts immunity and control COVID19. In anti-viral compounds, Remdesivir was found best and effective drug. Lopinavir also find effective drug next to Remdesivir. Hence in higher conditions, combination of remdesivir and lopinavir may be the best way of treatment for COVID19 patients. As antiviral compounds have side effects, Nimbin, Amlaic acid, Vitexin or Curcumin may be better molecules in the treatment of COVID19.

Introduction

Humans belonging to all age groups can be infected by the new emerged coronavirus (2019-nCoV/ COVID-19/ SARS-CoV-2). High probability of deaths exists with people having pre-existing medical conditions like diabetes, asthma and heart disease (Kaladhar, 2020). Most of the people who are infected with the COVID-19 virus with mild to moderate respiratory illness are recovered without special treatment due to good immunity. The focus of medical biologists is to explore innovations in research and provide advances in medical sciences at faster rate using bioinformatics tools (Kaladhar, 2011).

Large part to early Chinese efforts to genome sequencing of Sars-CoV-2, the virus that causes the Covid-19 disease, shared in early January 2020. More than 200 complete and partial genomes of bat out group Sars-CoV-2 are available in GISAID database (Guzzi et al., 2020). The phylogenetic methods with analyzing conserved sites can predict the probability and severity for the cause, spread and control measures of the disease. Many research groups all around the world are been working on mechanism of invading and controlling activity of coronavirus on human cells. The research goal on covid19 makes people to understand solutions of decreasing effects of virus along with drug/ vaccine development. Most of the primary host transfer of coronavirus is having travel history from different countries. Wuhan city in China is also having good air, road and train connections (Shang et al/. 2014) to different countries that can make human-to-human viral transmissions.

Covid-19
A novel coronavirus is an ongoing outbreak of novel coronavirus disease (COVID-19) with pneumonia, fever and respiratory symptoms emerged in Wuhan, China (Bai et al., 2020; Xu et al., 2020). The pathological symptoms of COVID-19 greatly resemble to previous coronaviruses like SARS (severe acute respiratory syndrome) and Middle Eastern respiratory syndrome (MERS) coronavirus infections.

Several microbial pathogenic diseases like Ebola, Zika, Nipah, and coronaviruses (CoV) are the novel diseases that were emerged in several geographical areas and spread worldwide. The emergence and spread of novel emerged coronavirus 2019 (2019-nCoV or COVID19) or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new public health crises threatening with challenges to control all around the world. The virus may be originated in bats and may be transmitted to humans from Wuhan, Hubei province, China in December 2019.

**Reasons of COVID19**

Viruses are the non-living particles outside living hosts that act as molecules stable for several years (Stanley, 1938). The stability is due to multiplication in bacterial cells present in the air, water or solid particles. The viruses effect as viral fevers whenever there is the changes in temperature and climate. The control of viral fevers will be depended based on the immunity and human molecular and physical factors like smoking, drinking, exercises, eating healthy foods, etc.

Coronaviruses are the large group of infectious viruses that affect the respiratory tract. The progression may be associated with extreme increase in inflammatory cytokines like IL2, IL7, IL10, MCP1, GCSF, IP10, MIP1A, and TNFα (Singhal, 2020). The research was previously supports that bats are responsible for covid19 transmission. Wuhan city and several countries has 5G network with several radiations like mobile radiations. The mobile data has electromagnetic spectrum that includes microwaves, visible light and X-rays. There is evidence that radiations causes mutations in several microbes like bacteria, fungi, viruses etc (Servomaa and Rytömaa, 1990; Diem et al., 2005).

The virus is originated in the seafood market from Wuhan, china, links to be due to eating infected bats or may also a bioweapon. The exact reasons have to be investigated in future.

**Symptoms and emergence**

The main early symptoms are dry cough, fever, headaches, chills, difficulty in breathing and a sore throat. Dry cough and sneeze are the general symptoms of air pollution. The symptoms of common cold are cough, mucus, sneeze and runny nose. The common symptoms of flu are cough, mucus, sneeze, runny nose, body ache, weakness and light fever. The common symptoms of coronavirus are dry cough, sneeze, body pain, weakness, high fever and difficulty in breathing. Hence based on symptoms, the patients will be primarily confirmed about SARS-CoV-2.

A 33 year old woman arrived at a hospital in Lanzhou, china (Travelled from Wuhan, China to Lanzhou had fever (102 degrees Fahrenheit), cough and coarse breathing for 5 days. The tests shown low WBC count, CT scan showed white patches in lower corner of lungs (ground glass opacity) and in short
period to thousands of people. The new coronavirus and SARS share about 80% of the genes. The sars-cov-2 virus was found 96% match from horseshoe bats from Yunnan. The rest 4% may be mutation of viral genome evolve through natural selection theory. A 55-year old individual from Hubei, China in November 2019 may suspect with sars-cov-2, originated in a bat and may be hopped to pangolin, and finally passed to human. Bats are consuming in various countries like African, Asian, European, Pacific countries like Vietnam, Seychelles, Indonesia, Thailand, Palau, China and Guam. Megabats may be a natural reservoir of Ebola virus. Several west African countries banned eating bats partially during 2013-2016 epidemic. Bats consume large amount of Cycad seeds and accumulate toxins to dangerous levels in the animal species. The megabats have several adaptations for flight, rapid oxygen consumption, sustain high heart beats (700 beats per minute), heat generation during flight, and large lung volumes. In past 45 years, apart from SARS-COV-19, Ebola, SARS, MERS (Middle Eastern Respiratory Syndrome) and Nipah has spread from Bats. Other viral diseases like Marburg virus disease (1967) and rabies virus disease (1996) also transmit through bats, Bats prefer warmer climate and can hibernate with high humidity and temperatures. Hence the coronavirus may also adapt to higher temperatures and can sustain due to natural mutation and adaptation.

Angiotensin converting enzyme II (ACE2) receptors exist in pigs, bats and civets also showed binding with SARS-cov-2 suggests, these animals may be responsible for infection (Zhou et al., 2020). Bats (Figure 1) harbour high proportions of zoonotic viruses and travel larger distances lead to mutation of SARS virus and emergence of novel coronavirus.

**Present treatment methods**

Antiviral therapy consisting drugs like ganciclovir, oseltamivir and lopinavir and ritonavir were given about 75% of cure in the patients. Avoiding close contact, washing hands frequently and improving immunity are the present precautions for COVID19. Patients are kept under Mechanical ventilation with lower tidal volumes (4 to 6 ml/kg predicted body weight, PBW) with lower inspiratory pressures, reaching a plateau pressure (Pplat) < 28 to 30 cm H$_2$O. PEEP should be as high as possible in order to maintain the driving pressure (Pplat-PEEP) as low as possible (< 14 cm H$_2$O). Medicinal compounds like lopinavir/ritonavir (400/100 mg every 12 hours), hydroxychloroquine (200 mg every 12 hours), chloroquine (500 mg every 12 hours), and Alpha-interferon (e.g., 5 million units by aerosol inhalation twice per day) are using as treatment levels (Cascella et al., 2020).

**Medicinal plants and antiviral drugs**

India has huge number of medicinal plants and the techniques for control of several diseases. The bacterial vaccines and antimicrobial drugs may used for prevention and treatment during the next pandemic. In 1918 influenza pandemic, therapeutic and preventive measures against influenza disease and production of influenza vaccine are the control measures taken at that time. The Spanish flu reached Sweden in June 1918. The pandemic of viral diseases would paralyze healthcare systems that results in high financial costs and rates of mortality.
As there are side effects from synthetic compounds, the natural medicinal compounds will provide better
cure along with boosting immunity. Hence *Phyllanthus amarus*, *Curcuma longa* , *Azardiricta indica*,
*Tinospora cordifolia*, *Allium sativum*, *Cynodon dactylon* and *Phyllanthus emblica* are selected as
important medicinal plants that can control the viral diseases like SARS-CoV-2. The important medicinal
compounds present in the plants have been shown in Table 1.

Table 1: Important medicinal compounds from plants for control of viral diseases

| Medicinal Compound      | Plant                  | Common name                        |
|-------------------------|------------------------|------------------------------------|
| 1-Heptacosanol (FDB004328) | *Tinospora cordifolia* | Amruthaballi or Giloy              |
| Ajoene (FDB011636)      | *Allium sativum*       | garlic                             |
| Amlaic acid (FDB015223) | *Phyllanthus emblica*  | Indian gooseberry or aml            |
| Curcumin (DB11672)      | *Curcuma longa*        | Turmeric                           |
| Furosin (Designed)      | *Phyllanthus amarus*   | Gale of the wind or Bhuamlaki      |
| Nimbin (Designed)       | *Azardiricta indica*   | Neem                               |
| Vitexin (Designed)      | *Cynodon dactylon*     | Bermuda grass or Arugampul         |

Selected Antiviral compounds that are effective in the treatment of viral diseases are shown in Table 2.

Table 2: Important Anti-viral drugs using for treatment of COVID19

| Antiviral Drugs | Treatment                                                  | Molecular Effect                               |
|----------------|------------------------------------------------------------|-----------------------------------------------|
| Camostat DB13729 | Antifibrinolytic Agents                                     | TMPRSS2                                       |
| Chloroquine DB00608 | Malaria                                               | ACE2 / Endosomal acidification               |
| Cyclosporine DB00091 | inflammatory and autoimmune conditions (isolated from the fungus *Beauveria nivea*) | Calcineurin-NFAT pathway                     |
| Disulfram DB00822 | treatment and management of chronic alcoholism            | PLpro                                         |
| Favipiravir DB12466 | resistant cases of influenza                              | targets RNA-dependent RNA polymerase (RdRp)  |
| Hydroxychloroquine DB01611 | malaria                                             | Endosomal acidification                        |
| Imatinib DB00619 | cancer                                              | endocytosis                                   |
| Lopinavir DB01601 | HIV-1 infection                                         | 3CLpro                                       |
| Nafamostat DB12598 | anticoagulant therapy                                   | TMPRSS2                                       |
| Remdesivir DB14761 | treatment for Ebola                                   | targets RNA-dependent RNA polymerase (RdRp)  |
| Ritonavir DB00503 | DB00503                                              | 3CLpro                                        |

The above compounds are tested with ACE2 and spike polyprotein for understanding better drug targets
in control of COVID19.

**Materials And Methods**

**Computer Specification**
Data Retrieval

The complete genome of Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1 with accession number NC_045512.2 was retrieved and was analysed for further studies.

Phylogenetic analysis

The genome of severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1 with accession number NC_045512.2 is submitted to BLASTp. The 29 genomes has been selected for understanding of conserved sites and finding relationships. The mutated regions of different genomes can also be identified based on non-finding of conserved sites.

Design of compounds

The 3D models of presented compounds from table 1 and 2 are retrieved from DrugBank (https://www.drugbank.ca/), Foodb (https://foodb.ca/) and some designed using ChemSW. The ligands are selected based on the 3D models (.pdb and .mol formats) that are retrieved or designed in the present work.

Design of receptor

The genome related to COVID-2019 has been retrieved from NCBI. As the entry of coronavirus is due to recognition of human receptors like ACE2 by SARS-CoV-2 viral spike glycoprotein, these molecules are selected as receptors. The protein structures are been designed using swissmodel.

Ligand receptor interaction studies

The activities of ligand receptor interactions is been studied using iGEMDOCKv2.1 software. The best model was selected based on the energy values obtained from iGEMDOCK.

Results And Discussion

Genomic relationship studies of SARS-CoV-2 provide better understanding about functional aspects of genomes. The sequences from Wuhan seafood market pneumonia virus had different point mutations and are showing non-conserved patterns in between sequences. Similarly the SARS-CoV2 sequences from USA were also shown nonconserved patterns. There are single character changes which show point mutations in the viral genomes. The colored patterns are shown in Figure 5.

The phylogenetic analysis showed in figure 6 provides an understanding that Viet Nam (VNM) deposited in ApR-2020 sequences are similar. The genome sequences of SARS-CoV2 from USA are also shown similarity. The viral genome sequences from Japan, Hong Kong, China and other regions had shown
difference in genome at least at one location making divergence in the phylogenetic tree. Hence the SARS-CoV-2 is mutating in entire genome by natural point mutation and spread fast to different countries in the world.

The docking studies for the control of COVID19 have been conducted by ligand-protein interaction studies using iGEMDOCKv2.1. The molecules can be applied for the best activities upon the selected receptors. The drug targets for the ACE2 and Spike polyproteins are selected based on the fitness values. The lower the value better is the stability and the activity of the medicinal compounds or drugs. The results have been shown in Table 3.

Table 3: Medicinal compound interaction studies with selected receptors for control of COVID19

| Medicinal Compound               | ACE Receptor | Spike Glycoprotein |
|----------------------------------|--------------|--------------------|
| 1-Heptacosanol (FDB004328)       | -99.00       | -75.05             |
| Ajoene (FDB011636)              | -69.713      | -65.73             |
| Amlaic acid (FDB015223)         | -113.54      | -105.6             |
| Curcumin (DB11672)              | -101.95      | -77.06             |
| Furosin (Designed)              | -96.68       | -83.1              |
| Nimbin(Designed)                | -109.38      | -110.58            |
| Vitexin(Designed)               | -115.06      | -98.93             |

The reports have shown that bioactive compounds like Nimbin present in Neem plant and Amlaic acid present in Amla are shown as best in the control COVID19. The bioactive compounds like Vitexin present in Bermuda grass and Curcumin present in turmeric powder were also shown good results. Hence usage of Neem, Amla, Bermuda grass and turmeric can boosts immunity and control COVID19.

Table 4 shows the active sites of the binded ligand with receptor

Table 4: Active sites of Medicinal compound interacted with selected receptors
Docking of Amla acid with ACE2 and Spike glycoprotein of SARS-CoV2 was shown in Figure 7.

The testing of best antiviral drugs was also predicted using \textit{in silico} analysis (Table 5).

Table 5: Interaction studies of Antiviral drugs with selected receptors for control of COVID19

| Antiviral Drugs | ACE2  | Spike Glycoprotein |
|----------------|-------|--------------------|
| Camostat DB13729 | -94.24 | -87.29 |
| Chloroquine DB00608 | -62.7 | -73.1 |
| Cyclosporine DB00091 | -83.75 | -136.54 |
| Disulfiram DB00822 | -50.39 | -63.81 |
| Favipiravir DB12466 | -87.1 | -69.5 |
| Hydroxychloroquine DB01611 | -82.55 | -71.45 |
| Imatinib DB00619 | -89.6 | -93.36 |
| Lopinavir DB01601 | -110.50 | -101.41 |
| Nafamostat DB12598 | -99.1 | -86.93 |
| Remdesivir DB14761 | -123.58 | -104.02 |
| Ritonavir DB00503 | -90.29 | -98.5 |

Table 5 shows the interaction of antiviral drugs with selected receptors causing COVID19, Remdesivir was found best and effective drug. Lopinavir also find effective drug next to Remdesivir. Hence in higher conditions, combination of remdesivir and lopinavir may be the best way of treatment for COVID19 patients.
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an RNA virus that causes coronavirus disease 2019 (COVID-19). Effective therapeutics and urgent treatments are needed to provide good health system worldwide. Most of the viruses that are emerged in last 40 years are not that much potent and effective but has been controlled due to less human developments. In the present decades, the radiations that are more adequate than required are generating, all wild creatures serving as food, high amounts of toxic compounds which are mutagenic are releasing into environments, deforestation and landminings are making abnormal conditions that may be leading to emergence of novel and potent viruses like SARS-CoV-2. The viral genome has point mutations at different locations in the entire genome that was evolved as powerful species in the year 2020.

### Table 6: Active sites of Antiviral drugs interacted with selected receptors

| Antiviral Drugs | ACE2 | Spike Glycoprotein |
|----------------|------|--------------------|
| Camostat DB13729 | H-M-GLU-233-H-M-ILE-234-H-M-HIS-242-V-M-GLN-241-V-M-GLN-241-V-M-GLU-247-V-M-LEU-248-V-S-LEU-248 | H-M-THR-724-H-S-THR-724-H-S-SER-729-V-M-THR-723-V-M-THR-724-V-M-GLN-926-V-S-GLN-926-V-M-ALA-930-V-S-LYS-933 |
| Chloroquine DB00608 | H-M-VAL-200-H-S-TYR-264-V-S-ILE-185-V-M-GLN-193-V-S-TYR-264-V-M-GLY-268 | H-M-TRP-353-H-S-ASN-354-V-M-ALA-352-V-M-TRP-353-V-M-TRP-353-V-M-ASN-354-V-M-ARG-355-V-M-ARG-355 |
| Cyclosporine DB00091 | H-M-SER-186-H-M-GLU-194-H-M-PRO-266-H-M-GLY-268-V-M-THR-95-V-S-ASN-99-V-M-LEU-176-V-S-ASN-188-V-S-HIS-207 | H-M-ILE-312-V-M-ASP-278-V-M-LEU-922-V-S-GLU-922-V-M-GLN-926-H-M-GLN-926-V-S-LYS-933 |
| Disulfiram DB00822 | V-M-THR-264-V-S-TYR-264-V-M-PRO-266-V-M-GLY-268 | V-M-THR-95-V-S-ASN-99-V-M-LEU-176-V-S-ASN-188-V-S-HIS-207 |
| Favipiravir DB12466 | H-M-GLU-233-H-S-GLU-233-H-M-ALA-238-H-M-CYS-240-V-M-GLU-247-V-M-LEU-248-V-S-LEU-248 | H-M-TRP-353-H-S-ASN-354-V-M-ALA-352-V-M-TRP-353-V-M-TRP-353-V-M-ASN-354-V-M-ARG-355-V-M-ARG-355 |
| Hydroxychloroquine DB01611 | H-S-ASN-244-V-S-ASP-278-V-S-ILE-185-V-M-THR-723-V-M-THR-724-V-S-GLN-926-V-S-LYS-933 | H-M-ILE-312-V-M-ASP-663-V-M-LEU-318-V-S-LYS-922-V-M-GLN-926-V-S-GLN-926-V-S-LYS-933 |
| Imatinib DB00619 | H-S-ASN-244-V-S-ASP-278-V-S-ILE-185-V-M-THR-723-V-M-THR-724-V-S-GLN-926-V-S-LYS-933 | H-M-ILE-312-V-M-ASP-663-V-M-LEU-318-V-S-LYS-922-V-M-GLN-926-V-S-GLN-926-V-S-LYS-933 |
| Lopinavir DB01601 | H-M-GLU-233-H-S-GLU-233-H-M-ALA-238-H-M-CYS-240-V-M-GLU-247-V-M-LEU-248-V-S-LEU-248 | H-M-ILE-312-V-M-ASP-278-V-M-LEU-922-V-S-GLU-922-V-M-GLN-926-V-S-GLN-926-V-S-LYS-933 |
| Nafamostat DB12598 | E-S-ASP-278-V-M-VAL-263-H-M-PRO-266-V-S-ILE-185-V-M-THR-724-V-M-THR-724-V-S-LEU-318-V-S-LYS-326 | H-M-ARG-44-H-S-TYR-170-V-M-LEU-226-V-M-THR-729-V-S-TYR-38-V-S-GLN-926-V-S-THR-726-V-S-THR-726-V-S-LYS-933 |
| Remdesivir DB14761 | H-S-ASN-244-V-S-ASP-278-V-S-ILE-185-V-M-THR-723-V-M-THR-724-V-S-LEU-318 | H-M-ILE-312-V-M-ASP-278-V-S-ILE-185-V-M-THR-724-V-M-THR-724-V-S-LEU-318 |
| Ritonavir DB00503 | H-S-ASN-244-V-S-ASP-278-V-S-ILE-185-V-M-THR-723-V-M-THR-724-V-M-THR-724-V-S-LEU-318 | H-M-ILE-312-V-M-ASP-278-V-S-ILE-185-V-M-THR-724-V-M-THR-724-V-S-LEU-318 |

**Conclusion**
COVID19 is a flexible mutant that can transform from one genome to other due to radiation. The activities of any virus can be only controlled by medicinal compounds present in medicinal plants. Hence the best drug identification is important along with social distancing. The present research work can provide better drug from the available medicinal plants in India. Remdesivir and Lopinavir was found best and effective anti-viral drugs. As the anti-viral drugs are having side effects, alternately natural compounds like Nimbin present in Neem plant, Amlaic acid present in Amla, Vitexin present in Bermuda grass and Curcumin present in turmeric powder were also shown good results with COVID-19.

Declarations

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Conflict Of Interests

There is no known conflict of interest associated with the publication

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**Figures**

![Figure 1](image_url)

**Figure 1**

Bats containing coronaviruses
Figure 2

Important medicinal compounds from plants for control of viral diseases
Figure 3

Important Anti-viral drugs using for treatment of COVID19

Figure 4

Angiotensin converting enzyme II (ACE2) receptor

SARS-CoV-2 viral spike glycoprotein
Selected Receptors in present study

Figure 5

Colour patterns with mutations in selected SARS-CoV2 virus
Figure 6

Phylogenetic tree of different genomes of SARS-CoV2
Figure 7
Docking of Amlaic acid with ACE2 and Spike glycoprotein of SARS-CoV2

Figure 8
Docking of Remdesivir with ACE2 and Spike glycoprotein of SARS-CoV2