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A Web-Based Platform on Coronavirus Disease-19 to Maintain Predicted Diagnostic, Drug, and Vaccine Candidates

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A web-based resource CoronaVIR (https://webs.iiitd.edu.in/raghava/coronavir/) has been developed to maintain the predicted and existing information on coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We have integrated multiple modules, including ''Genomics,'' ''Diagnosis,'' ''Immunotherapy,'' and ''Drug Designing'' to understand the holistic view of this pandemic medical disaster. The genomics module provides genomic information of different strains of this virus to understand genomic level alterations. The diagnosis module includes detailed information on currently-in-use diagnostics tests as well as five novel universal primer sets predicted using *in silico* tools. The Immunotherapy module provides information on epitope-based potential vaccine candidates (e.g., LQLPQGTTLPKGFYA, VILLNKHIDAYKTFPPTEPKKDK KKK, EITVATSRTLS, GKGQQQQGQTV, SELVIGAVILR) predicted using state-of-the-art software and resources in the field of immune informatics. These epitopes have the potential to activate both adaptive (e.g., B cell and T cell) and innate (e.g., vaccine adjuvants) immune systems as well as suitable for all strains of SARS-CoV-2. Besides, we have also predicted potential candidates for siRNA-based therapy and RNA-based vaccine adjuvants. The drug designing module maintains information about potential drug targets, tertiary structures, and potential drug molecules. These potential drug molecules were identified from FDA-approved drugs using the docking-based approach. We also compiled information from the literature and Internet on potential drugs, repurposing drugs, and monoclonal antibodies. To understand host–virus interaction, we identified cell-penetrating peptides in the virus. In this study, state-of-the-art techniques have been used for predicting the potential candidates for diagnostics and therapeutics.

Keywords: COVID-19, SARS-CoV-2, resource, corona, vaccine, drug

Introduction

The year 2019 ended with the outbreak of a new disease called pneumonia of an unknown cause that occurred in China.[1] Several independent laboratories identified the causative agent of this enigmatic pneumonia as a novel coronavirus, which has been named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease caused by this has been named as coronavirus disease-19 (COVID-19).[2–4] The World Health Organization (WHO) has declared this outbreak as pandemic because the virus has spread across the globe and infected millions of people within months of its emergence. As of October 11, 2020, >37 million people are reported as infected with COVID-19. With this high rate of increase of this infection, the damage has reached an alarming number of >1 million deaths worldwide and with >0.2 million deaths in the United States alone (https://www.worldometers.info/coronavirus/).

SARS-CoV-2 belongs to a family of coronaviruses, which are highly diverse, enveloped, positive-sense, and single-stranded RNA viruses.[5] It shares 79.5% sequence identity with SARS-CoV-1 and 96.2% identity with bat CoV RaTG13.[6] The phylogenetic analysis indicates that SARS-CoV-2 belongs to subgenus *Sarbecovirus* of the genus *Betacoronavirus* and is distinct from SARS-CoV-1.[2–4] SARS-CoV-2 is a new strain of coronavirus that is the seventh member of the family of coronaviruses to infect humans, after Middle East respiratory syndrome (MERS)-CoV and SARS-

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CoV-1. It has been shown in recent studies that this new strain uses the same cell receptor, that is, angiotensin-converting enzyme 2 (ACE2), for the entry into the host cell as used by earlier strains of coronavirus.[7,8] Wan et al. suggested that the single N501T mutation in spike protein of SARS-CoV-2 probably significantly enhanced its binding affinity for ACE2.[9]

The exact mechanism of action for SARS-CoV-2 is still needed to be discovered.[10] Recent studies have shown that elevated levels of proinflammatory cytokines (e.g., IL-1, IL-6, IL-8, and IL-12) cause severer respiratory infections, which leads to viral pneumonia and acute respiratory distress syndrome in some COVID-19 patients.[11] These uncontrolled SARS-CoV-2 infections may target massive cytokine storm, in which some chemokines and proinflammatory cytokines (TNF-α, IL-1β, and IL-6) are intensely expressed by the immune system, which leads to multisystem organ failure and to increased mortality rate.[12,13] We have recently developed a method IL6Pred, which can predict IL-6 inducing peptides/epitopes (https://webs.iiitd.edu.in/raghava/il6pred/). IL6Pred tool can be helpful to the scientific community, working in the field of vaccine designing against COVID-19.[14]

In addition, the early diagnosis suggests that SARS-CoV-2 infections are strongly associated with cardiovascular disease.[15–18] Furthermore, it also promotes the development of cardiovascular disorders such as heart failure,[19] acute coronary syndrome,[20] myocardial injury,[21] and venous thromboembolism.[22]

Owing to the pandemic nature of the COVID-19 outbreak and the increase in global incidences, consistent efforts are going on to contain the situation and manage the infected patients. Although there has been an exponential rise in the research studies, no effective treatment or vaccine is yet available for COVID-19. However, several clinical trials have been proposed or are ongoing.[23]

The majority of these trials are being conducted all over the world. Some of the vaccines such as Ad5-nCoV, AZD1222, CoronaVac, and mRNA-1273 are in phase 3 of clinical trials.[24] Apart from these, various standard therapies such as antipyretic therapy, oxygen therapy, renal replacement therapy, and drugs related to SARS such as oseltamivir, the combination of interferon-α and lopinavir/ritonavir are in current clinical use for managing infected patients.[25] It is also crucial to note that the current progress in the coronavirus vaccine research would not have been possible without the endeavor of clinical bioinformaticians working behind closed doors. With the elucidation of the SARS-CoV-2 biological sequence, there have been numerous attempts to understand the virus at the molecular scale, which has led to the development of various *in silico* tools and resources notably.[26] Many online dashboards were developed by researchers such as at John Hopkins CSSE, which can be further used to track the COVID-19 cases in real time and also for other essential statistics.[27]

An individual researcher or research group or even a single institute has insufficient resources and knowledge to provide a time-bound solution against a pandemic (e.g., COVID-19). To provide effective solutions against a deadly disease in a limited time, one should generate and promote open-source resources. These resources can be used by experimental researchers and clinicians to provide ultimate solutions against any epidemic or pandemic. In this study, we developed a platform that offers computer-aided solutions to manage COVID-19. These resources are generated using state-of-the-art techniques in the field of bioinformatics. These computer-aided solutions include primers for diagnosis and molecules for therapeutic (drugs and vaccine). Moreover, to track the COVID-19 instances worldwide, we have also developed the online dashboard. To facilitate the scientific community, we provide a web-based platform named CoronaVIR.

Materials and Methods

General information

There is a variety of relevant information regarding the SARS-CoV-2 and its resulting COVID-19. This information is scattered in different forms such as literature, web resources, and databases. We performed a keyword search on the Google search engine using different terms relevant to SARS-CoV-2 and COVID-19. We manually evaluate these links obtained from Google search to identify authenticated information. Finally, important and authenticated links, videos, and documents were compiled and integrated into CoronaVIR.

Genomic and proteomic data collection

The whole-genome and proteome sequences of SARS-CoV-2 were retrieved from the National Center for Biotechnology Information.

We have obtained 53 genome sequences of SARS-CoV-2 strains from NCBI (https://www.ncbi.nlm.nih.gov/nuccore/MN908947). Besides, a total of 10 protein sequences of the Wuhan genome (accession ID MN908947.3) were extracted at the time this study started.

Diagnosis

First, PubMed and Google search engines were mined using keywords such as ''2019-nCoV Diagnosis,'' ''Diagnostic Primers,'' ''2019-nCoV,'' and ''COVID-19.''. This information was used to identify 12 diagnostic assays and primers (primer combinations) from four publications, reported till March 1, 2020. Second, we downloaded 53 complete genomes (accession ID with other information such as strain and source country given in Supplementary Table S1) and 40 nucleotide sequences of the five genes (N, E, M, ORF1ab, and ORF1ab-RdRP) of COVID-19 from the NCBI Virus Resource (https://www.ncbi.nlm.nih.gov/labs/virus/vssi/#/) at the time this study started. Third, we designed primers corresponding to whole-genome and specific genes using the Primer3_core tool,[28] (https://github.com/primer3-org/primer3) with default parameters. Notably, we have generated primers for each of the sequences individually in case there are multiple sequences present for any of the genes. Subsequently, we removed duplicate primer pairs for each of the sequences or genes. In addition, we also compiled the diagnostic primers of other strains of coronavirus from the MRPrimerV,[29] a public database of primers for viruses. Besides, we have also collected and compiled the information regarding the various diagnostic tests for COVID-19 from the literature.

Vaccine design

To identify potential peptides that could serve as vaccine candidates, we generated all possible 9-mer peptides from

different proteins of SARS-CoV-2 (accession no. MN908947). A wide range of immune informatics tools have been used to predict B cell epitopes, T cell epitopes, major histocompatibility complex (MHC) binders, and vaccine adjuvants.

B cell epitopes. In this study, LBtope[30] has been used to predict B cell epitopes from the mentioned 9-mer peptides of the different proteins of SARS-CoV-2. LBtope is a highly efficient method that is built and trained on the vast data set of B cell epitopes and nonepitopes that were experimentally validated and implemented in numerous studies.[31–35] The prediction was made with the default threshold of 60% cutoff, which was also previously used by Gupta et al. for designing epitopes for the Zika virus.[36]

T cell epitopes. To predict cytotoxic T lymphocytes (CTLs), we used the immune informatics tool CTLPred.[37] It is a direct method that is based on the primary sequence of the antigens for predicting the CTL epitopes rather than predicting the MHC class I binders. It has implemented machine learning techniques such as an artificial neural network (ANN) and support vector machine (SVM). In this study, CTL epitopes were predicted using the ANN module of the CTLpred with the default parameters and with the cutoff score of 0.51.

Promiscuous MHC binders. The MHC plays a crucial role in the human immune system. It expresses on the cell surface and binds to the antigenic peptides. Subsequently, it presents the peptide to activate the T cells. In this study, potential MHC class I and class II binders were identified using ProPred 1[38] and ProPred,[39] respectively. The prediction was made with the default parameters, that is, 4% threshold for ProPred 1 to predict MHC class I binders and 3% threshold for ProPred for predicting MHC class II binders. We identified promiscuous MHC binders that can bind to a large number of MHC alleles.

Experimentally validated epitopes. The Immune Epitope Database (IEDB)[40] is the repository that contains a significant number of experimentally validated epitopes or antigenic regions that tend to modulate the immune system. Therefore, with an aim to identify only those epitopes of SARS-CoV-2 that have already been characterized in the past, we have mapped the epitopes predicted in our study with the experimentally proven IEDB epitopes. To further narrow down the search, we have used different filters, that is, coronavirus as source organisms and coronavirus protein as antigen name to extract the epitopes.

Vaccine adjuvants. We have used VaxinPAD[41] to identify the potential peptide-based vaccine adjuvants. It is used to predict the immunomodulatory peptides or antigen-presenting cell epitopes (A-cell epitopes). For determining the potential peptide-based vaccine adjuvants, we have used the SVM-based model with the threshold of −0.5. In addition to peptide-based vaccine adjuvants, we predicted nucleotide-based vaccine adjuvants from genes of 10 proteins (Supplementary Table S2) of SARS-CoV-2 (accession ID MN908947). In this study, we used the ''Batch Mode'' of VaccineDA with default parameters[42]; the length of adjuvants is 30 nucleotides.

RNA therapeutics

To design siRNA-based therapeutics against the SARS-CoV-2 strain, we generated 19mer oligonucleotide from the corresponding mRNA sequences (accession ID MN908947), as this length is considered to be sufficient to silence the cognate mRNA target sequence. Previously, many of the prediction methods were developed based on the 19mer length of the siRNA sequence.[43–46] To identify which siRNA oligonucleotide could serve as an efficient siRNA against the SARS-CoV-2, we predicted the efficacy of each of oligonucleotides (siRNA) using ''DesiRm'' software with default parameters.[45] Eventually, we have extracted the highly potent siRNAs (having efficacy >0.80 value) and target accessibility of 0.60.

Drug designing

In this platform, we integrated the ''Drug Designing'' module, which elucidates various aspects related to the designing of potential drug candidates for the treatment of COVID-19. In this study, mainly four submodules have been implemented, namely, potential drug target, three-dimensional (3D) structure, potential drug molecule, and cell-penetrating peptides.

Potential drug targets

This submodule provides details about potential drug targets that could be used for designing drugs. This new strain, that is, SARS-CoV-2, shares high sequence similarity (up to 96%) with the previous strains, that is, MERS, SARS, and Bat-SARS coronavirus,[3,6,10] and hence, the chances of having the same drug targets are higher. Therefore, based on literature search and previous studies,[3,6] we have provided the details of some of the probable drug targets such as target name, sequence, and locus tag. This complete information was extracted from the complete reference genome sequence of Wuhan coronavirus (accession ID NC_045512.2).

Tertiary structure

One of the prerequisites for designing drugs is the availability of tertiary or 3D structures of drug targets. SARS-CoV-2 encodes several proteins that could act as potential drug targets; however, 3D structures of only selective proteins such as spike glycoprotein (PDB ID: 6VSB) and nucleocapsid phosphoprotein (PDB ID: 6VYO) are available in the Protein Data Bank (PDB). We predict the 3D structures of the SARS-CoV-2 proteins using Phyre 2.0 server.[47] Toward this, protein sequences were extracted for the complete genome of SARS-CoV-2 (NCBI reference NC_045512.2) from NCBI. Phyre 2.0 is a homology-based software for predicting the 3D structure of a protein. Default parameters were used while predicting the structures except for modeling mode, which was set to intensive instead of normal. The quality assessment of the predicted structures was performed using PROCHECK[48] and QMEAN software.[49] These structures can be used for docking studies for designing new inhibitors.

Potential drug molecule

An extensive search was performed in different databases such as Pubmed and DrugBank[50–52] to identify potential

drugs. As there is no FDA-approved drug specifically for COVID-19 till today, we look for the drugs that have already been approved for the viruses similar to SARS-CoV-2, such as SARS and MERS. The logic behind this approach was based on the similarity of the genomic layout and the cellular and molecular biology of these viruses.

In addition, we used the PatchDock server[53,54] for docking the putative drug molecules to their targets. The parameters used for docking were ''clustering RMSD'' as 4.0 and ''complex type'' as the protein small ligand. Modeled protein drug structures were further analyzed using PyMOL software.[55]

Cell-penetrating peptides

It is important to identify cell-penetrating peptides in SARS-CoV-2 proteins to understand the mechanism of host–virus interaction. Cell-penetrating peptides in viral proteins help the virus to enter into the cell of the host. In addition, cell-penetrating peptides can be used for drug delivery. In the past, most of the cell-penetrating peptides were discovered from viral proteins; for example, widely used transactivating transcriptional activator peptides were discovered from HIV.[56,57] In this study, we used CellPPD[58] to predict the cell-penetrating peptides in SARS-CoV-2; each peptide has 10 amino acids. Different physicochemical properties such as hydrophobicity, charge, and molecular weight of the peptides were also computed. Based on the SVM scores, we selected the top 10 cell-penetrating peptides (CPPs) from different viral proteins, which could be used as vehicles for drug delivery. The higher the SVM score, the more likely the peptide is to be a CPP.

Web server implementation

CoronaVIR has been developed using HTML, PHP 5.2.9, and JAVA scripts. A responsive website based on HTML5 has been used to make the website compatible with mobiles and tablets.

Results

General information

In this study, we have developed a comprehensive web-based resource named ''CoronaVIR'' for SARS-CoV-2 or COVID-19. As shown in Figure 1, information has been organized into five modules or categories. First, the module provides general information about this virus and disease. In this study we collected and compiled vital information from a wide range of resources, including literature. In addition, we have used various *in silico* techniques to identify potential diagnostic primers, peptide-based vaccine candidates, and potential drug molecules. The overall architecture of the resource is shown in Figure 1. Each of the sections is described hereunder in detail.

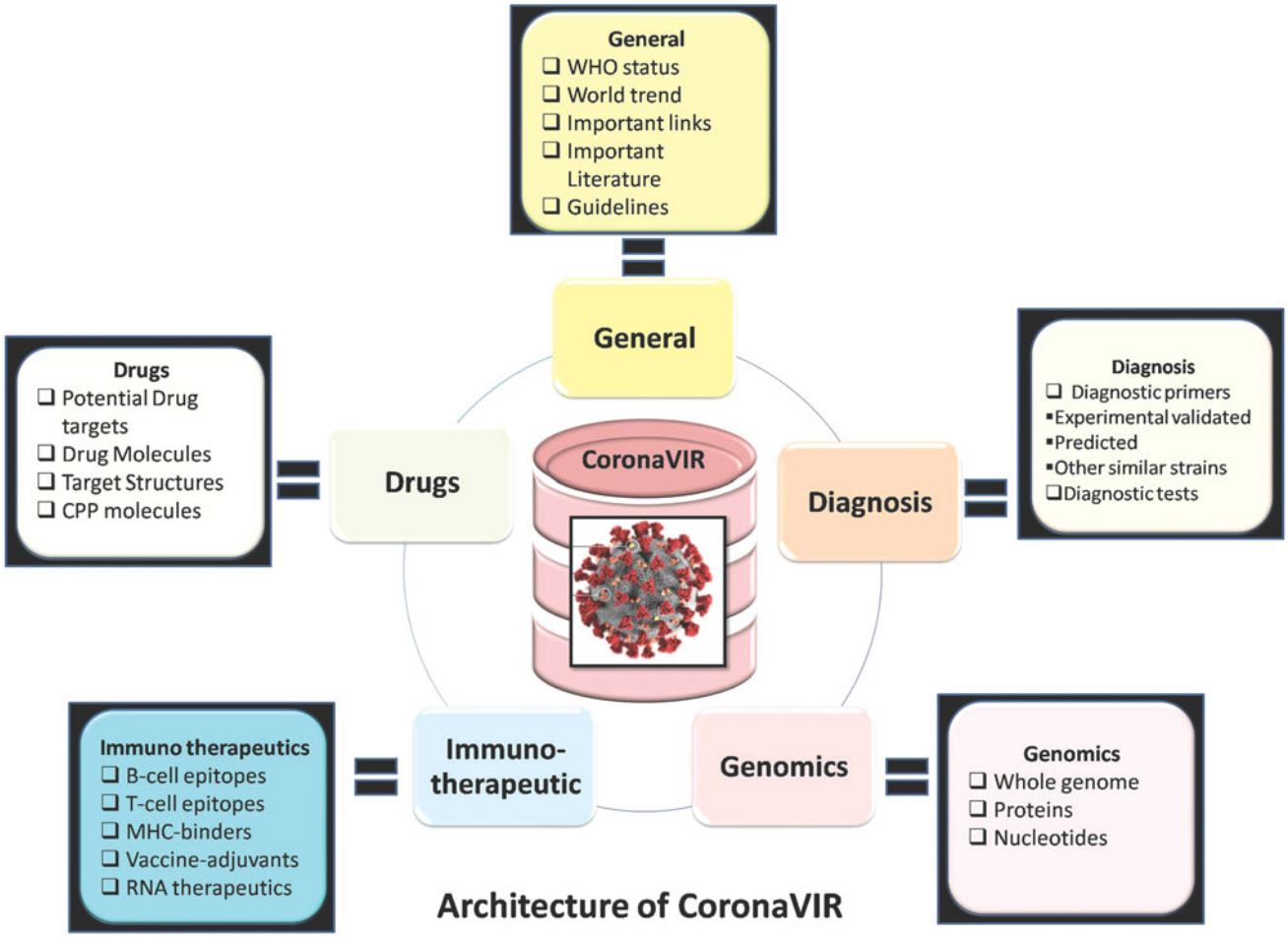

FIG. 1. The overall architecture of CoronaVIR.

Genomics module

The 53 genome sequences of SARS-CoV-2 strains were submitted by different groups from various regions worldwide. It includes 25 from China, 19 from the United States, and 2 each from India and Taiwan (Supplementary Table S1). To facilitate community, we have provided comprehensive information on these genomes that includes strain name, size, and accession ID. In addition, the source such as NCBI resource has been linked. Ten protein sequences were manually checked for the presence and absence of well-reported open-reading frames (ORFs) and thereafter categorized. These 10 proteins are Orf1ab polyprotein, Orf3a protein, envelope protein (E), Orf6 protein, Orf7a protein, Orf8 protein, Orf10 protein, spike protein, membrane glycoprotein and nucleocaspid phosphoprotein. We have also provided the important links or URLs of NCBI virus genomic resources on the web server to obtain the latest and updated information regarding genomes.

Diagnosis and current therapeutics

Diagnosis module

Diagnostic primers. This section provides information about 12 experimentally validated primer pairs collected from the literature. In addition, this section also contains information about 65 unique predicted primer pairs. Following is the distribution of these predicted primers: (i) 5 pairs for complete genome, (ii) 20 for N-gene and ORF1ab-RdRP, (iii) 10 for ORF1ab, and (iv) 5 each for M-gene and E-gene of COVID-19. We named five pairs of primers, which were designated from the complete genome as ''universal primers,'' as they are found to be common among all the 53 different genome sequences, given in Table 1. In the case of experimentally validated primers, we have provided the gene symbol of the gene against which primers designated, sequences, Tm, and GC content (%) of forward (Fwd) primers, reverse (Rev) primers, and probes (oligo). Experimental assay conditions such as Tm and concentration are also provided along with the reference study, specific comments regarding their experimental condition, or result inference from the respective study. In the case of predicted primers, we have provided information such as nucleotide sequences, Tm, and GC content (%) of the forward (Fwd) primers, reverse (Rev) primers, and probes (oligo). Besides, we have also provided information such as the ID and country of source sequence, with gene symbols. Furthermore, we have also compiled information (e.g., sequences, TM, GC contents, and quality score) for 296 primer pairs for other strains of the coronavirus, obtained from the ''MRPrimerV.'' The detailed information related to all primer sets can be found on the ''Diagnostic Primers'' submodule under the ''Diagnosis'' module on the web server (https://webs.iiitd.edu.in/raghava/coronavir/prim.php).

Diagnostic tests. This section provides the detailed information of all the possible diagnostic tests that can be carried out for the diagnosis of COVID-19. These guidelines contain the procedures to perform diagnosis through real time-polymerase chain reaction (RT-PCR) assay which is the most common diagnostic test used under the current scenario and CRISPR-Cas12–based assay. Besides, this module also gives information about monitoring several biomarkers to predict

Table 1. Potential Candidates for Universal Diagnostic Primer Sets for Coronavirus Disease-19 (Predicted Using Primer3_core), Which Are common Among 53 Different Genome Sequences (Obtained from NCBI Virus Resource)

Fwd seq	*Rev seq*	*Oligo*	*Fwd Tm*	*Rev Tm*	*Oligo Tm*	*Fwd GC*	*Rev GC*	*Oligo GC*	*Target size*
CTCTTCTCGTTCCTCATCACG	CCAGACATTTTGCTCTCAAGC	TTGCTGCTGCTTGACAGATT	59.99	60.01	59.75	52.38	47.62	45	162
AGTCAAGCCTCTTCTCGTTCC	CCAGACATTTTGCTCTCAAGC	TTGCTGCTGCTTGACAGATT	60.01	60.01	59.75	52.38	47.62	45	170
GTCAAGCCTCTTCTCGTTCCT	CCAGACATTTTGCTCTCAAGC	TTGCTGCTGCTTGACAGATT	60.01	60.01	59.75	52.38	47.62	45	169
AGCCTCTTCTCGTTCCTCATC	CCAGACATTTTGCTCTCAAGC	TTGCTGCTGCTTGACAGATT	59.97	60.01	59.75	52.38	47.62	45	165
GGGGACAACCAATCACTAAT	TAACCTTTCCACATACCGCAG	CAGTTACACCGGAAGCCAAT	59.93	60.01	59.99	47.62	47.62	50	278

COVID-19, coronavirus disease-19; Fwd, forward primer; GC, GC content (% age); Rev, reverse primers; seq, sequence; Tm, melting temperature.

severe and fatal COVID-19. All the specified information is collected from the recent literature.[59–61] But, there are several challenges and limitations regarding these diagnostic tests. For instance, the molecular tests for COVID-19 diagnosis developed till yet are complex, costly, slow, and can be carried out only by qualified clinical laboratory personnel. In case of RT-PCR, factors such as quality of extracted RNA, degradation of purified RNA, or presence of RT-PCR inhibitors may give false negative results.[62] The tests need processing and analysis from manufacturer and cannot be done at the sample collection site or hospital, leading to potential modes of failure during specimen storage and transport.

Immunotherapy or vaccine design module

Peptide-based therapeutics. In this study, we have predicted potential coronavirus epitopes, which include B cell epitopes, T cell epitopes, and MHC class I and class II binders. A total of 594 B cell epitopes and 966 T cell epitopes predicted, which have ≥60% probability of correct prediction, are shown on the website with their peptide sequences. In addition, 31,215 MHC class I and 17,635 MHC class II binders were predicted using ProPred 1 and ProPred, respectively, and are displayed on the website. Apart from that, 117 experimentally validated IEDB epitopes were mapped to corona antigens, which include B cell and T cell assays. The assay information includes PubMed ID, epitope description, host organism, technique used, assay group, and qualitative measure.

Potential vaccine candidates

In this study, we have suggested 17 epitopes that can act as potential vaccine candidates against SARS-CoV-2 based on the results of different prediction methods. The epitopes that were conserved among different prediction tools such as LBtope, CTLPred, VaxinPAD, ProPred 1, and ProPred as well as experimentally validated by IEDB were chosen as potential vaccine candidates, as given in Table 2. Besides, we have linked these epitopes on our web server, ''CoronaVIR,'' to the source page of IEDB (https://webs.iiitd.edu.in/raghava/coronavir/map.php). Furthermore, by clicking on ID, the user can get complete information regarding the epitope, organism, antigen, assays used, etc. Out of these 17 vaccine candidates, 5 epitopes, that is, LQLPQGTTLPKGFYA, VILLNKHIDAYKTFPPTEPKKDKKKK, EITVATSRTLS, GKGQQQQGQTV, and SELVIGAVILR, are reported in IEDB (B cell and T cell assays), LBtope, CTLPred, VaxinPAD, ProPred, and Propred 1.

Mapping and validation of predicted epitopes in strains of various countries

Next, we aimed to validate our peptide-based potential vaccine candidates in other strains across the globe. Toward this, we randomly took six different genomes from different countries available for SARS-CoV-2 strains from NCBI with accession IDs MT012098, MT050493, MT066156, MT159711, MT246462, and MT233519. Subsequently, we mapped our top five peptide-based vaccine candidates. Mapping results showed that these epitopes are present in all these strains, given in Table 3. These results indicate that these vaccine candidates can be implemented widely across the globe.

Nucleotide-based adjuvants. First, we predicted a large number of nucleotide-based vaccine adjuvants for each of 10 proteins using VaccineDA, as given in Supplementary Table S2 and on the web server (https://webs.iiitd.edu.in/raghava/coronavir/adj.php). Subsequently, the top 10 potential vaccine adjuvant candidates were selected based on the SVM score, enlisted in Table 4. Out of them, oligodeoxynucleotide of Orf8 and Orf1ab, that is, ''GCGTTGTTCGT TCTATGAAGACTTTTTAGA'' and ''ACGTTAATACGT TTTCATCAACTTTTAACG,'' withstands to be exceptionally immunomodulator with the SVM score of 1.885 and 1.537, respectively.

RNA therapeutics

This section maintains a list of potential siRNAs that can serve as candidates for RNA-based therapeutics. As given in Table 5, these siRNAs can suppress or degrade different genes of SARS-CoV-2 with high efficacy (>0.80): each siRNA has high target accessibility (>0.6). In this study, we have shown only the top 10 siRNAs that can serve as a therapeutic candidate against COVID-19. Among them, Orf1ab protein is shown to be the top protein with the predicted antisense sequence of siRNA ''AAAUUGAUCGUAC AACACG'' and mRNA target sequence ''CGUGUUGUAC GAUCAAUUU'' with target accessibility of 0.636979 and efficacy of 1.129115.

Drug designing module

Drug targets. In previous studies, it has been shown that some of the potential viral drug targets include nonstructural proteins (papain-like protease, RNA-dependent RNA polymerase, helicase, etc.), structural proteins (nucleocapsid protein, envelope protein, and spike protein), and other accessory proteins.[63,64] As SARS-CoV-2 also has a positive-sense single-stranded RNA as its genetic material, therefore, we compiled this information about these targets for SARS-CoV-2. Thus, we selected the potential drug targets, which are key components of the COVID-19 infection lifecycle. This includes proteins involved in the viral entry into the host cell, viral replication machinery, and viral RNA synthesis. The information includes accession ID, gene encoding the protein, locus tag, source of the protein, protein sequence, and identical proteins. All this information can be accessed from the web server (https://webs.iiitd.edu.in/raghava/coronavir/dt.php).

3D structure

As per RCSB-PDB data till March 25, >90 crystallized structures related to SARS-CoV-2 have been reported. On our web server, first, we maintained some of the important structures that include crystallized structures of spike glycoprotein (PDB ID: 6VSB), HR2 domain of 2019-nCoV (PDB ID: 6LVN), the postfusion core of SARS-CoV-2 S2 subunit (PDB ID: 6LXT), and crystal structure of the main protease in association with an inhibitor N3 (PDB ID: 6LU7). Besides, Phyre2.0 server[47] was used for modeling the structures of various other proteins. In this study, we modeled 10 important proteins that include RNA-dependent RNA polymerase, envelop protein, membrane glycoprotein, nucleocapsid phosphoprotein, and ORF3a protein, which could

Table 2. Potential Vaccine Candidates Include IEDB (B Cell and T Cell Assay), B Cell Epitope, T Cell Epitope, Vaccine Adjuvants, MHC Class I and II Binders

Protein	*Potential vaccine candidate*	*IEDB (T cell) (#1)*	*IEDB (B cell) (#1)*	*B cell epitope (#2)*	*T cell epitope (#3)*	*Vaccine adjuvants (#4)*	*MHC class I (#5)*	*MHC class II (#6)*
Nucleocapsid phosphoprotein	LQLPQGTTLPKGFYA	✓	✓	✓	✓	✘	✓	✓
Nucleocapsid phosphoprotein	VILLNKHIDAYKTFPPTEPKKDKKKK	✓	✓	✓	✓	✘	✓	✓
Membrane glycoprotein	EITVATSRTLS	✓	✓	✓	✓	✘	✓	✓
Nucleocapsid phosphoprotein	GKGQQQQGQTV	✓	✓	✓	✓	✘	✓	✘
Membrane glycoprotein	SELVIGAVILR	✘	✓	✓	✓	✓	✓	✓
Envelope protein	ALRLCAYCCN	✓	✘	✓	✓	✓	✓	✓
ORF6	HLVDFQVTIAEILLIIMR	✓	✘	✓	✓	✘	✓	✓
Envelope protein	VFLLVTLAILTALRLCAYCCNI	✓	✘	✓	✓	✓	✓	✓
Membrane glycoprotein	NGTITVEELKKLLEQWNLVIGFLFL	✓	✘	✓	✓	✓	✓	✓
Membrane glycoprotein	ASFRLFARTRSMWSFNPETNILLNVPLHGT	✓	✘	✘	✓	✓	✓	✓
Membrane glycoprotein	SRYRIGNYKL	✓	✘	✘	✓	✓	✓	✓
ORF8	RCSFYEDFLEYHDVR	✘	✘	✓	✓	✓	✓	✓
ORF6	IWNLDYIINLIIKNLSKSLT	✘	✘	✓	✓	✘	✓	✓
Surface glycoprotein	SETKCTLKSFTVEKGIYQTSNF	✘	✘	✓	✓	✘	✓	✓
ORF8	MKFLVFLGIITTVAAFHQECSLQSCTQ	✘	✘	✓	✓	✘	✓	✓
ORF3a	DGTTSPISE	✘	✘	✓	✓	✘	✓	✘
ORF3a	SKIITLKKRWQLALSKGVHFVCNLLL	✘	✘	✓	✓	✓	✓	✘

#1, IEDB; #2, LBtope; #3, CTLPred; #4, VaxinPAD; #5, ProPred 1; #6, ProPred.
IEDB, Immune Epitope Database; MHC, major histocompatibility complex.

TABLE 3. MAPPING AND VALIDATION OF PREDICTED EPITOPES IN SARS-COV-3 STRAINS FROM OTHER PARTS OF GLOBE

Epitope	*Protein*	*Accession IDs and country*					
		MT012098 India	*MT050493 India*	*MT066156 Italy*	*MT159711 United States*	*MT246462 United States*	*MT233519 Spain*
LQLPQGTTLPKGFYA	Nucleocapsid phosphoprotein	Yes	Yes	Yes	Yes	Yes	Yes
VILLNKHIDAYKTFPPTEPKKDKKKK	Nucleocapsid phosphoprotein	Yes	Yes	Yes	Yes	Yes	Yes
EITVATSRTLS	Membrane glycoprotein	Yes	Yes	Yes	Yes	Yes	Yes
GKGQQQQGQTV	Nucleocapsid phosphoprotein	Yes	Yes	Yes	Yes	Yes	Yes
SELVIGAVILR	Membrane glycoprotein	Yes	Yes	Yes	Yes	Yes	Yes

be potential drug targets, as represented at web server (https://webs.iiitd.edu.in/raghava/coronavir/struct2.php). We observed that our modeled structures were of good quality as most of the protein residues are present in the allowed region (here we consider most favored regions, additionally allowed regions, and generously allowed regions). Also, the QMEAN score, which is measured in the range of 0–1, was found to be present >0.5 for most of the residues. Overall, the model is good enough for drug designing studies. Detailed information of the structures such as template information, the percentage identity of the query sequence with the template sequence, type of fold present in the template, etc., has been provided for more information. Users can download the structures and the Ramachandran Plot from the link (https://webs.iiitd.edu.in/raghava/coronavir/struct.php).

Potential drug molecules

We mapped the SARS-CoV-2 genome to existing FDA-approved drugs present in the DrugBank. This leads to the identification of drugs (e.g., camostat myselate, ritonavir, lopinavir, remdesivir, and chloroquine) that have the potential to treat COVID-19. These drugs have been previously proposed to treat various viral infections.[65–67] HIV protease inhibitors Ritonavir and Lopinavir are currently under clinical trials for treating COVID-19 infection, and in some patients, it has shown some promising results. Furthermore, we have also performed the docking procedure by docking the putative drugs on the predicted structures of the targets from SARS-CoV-2. To compare our docked structures, we have also docked the drugs with their targets given in Drugbank,[50–52] whose structures are available in PBD.[68] We found that gs-6620, which is similar to remdesivir, got the highest score among all. Table 6 represents a list of some of the potential drugs along with their target information. We have also compiled the list of drugs that have been predicted computationally or are repurposed drugs from different studies. The list is provided on our website. Besides, Dong et al. have suggested the five antiviral drugs included in the guidelines (version 6) for treatment of COVID-19, available on the web server.[27] Users can browse those drugs by clicking on the ''Click to view complete file'' tab provided at the website (https://webs.iiitd.edu.in/raghava/coronavir/dm.php).

Drug delivery

We predicted CPPs corresponding to 10 proteins of the SARS-CoV-2 using the CellPPD server.[58] These peptides can be used for drug delivery. In addition, these peptides can be used to understand virus–host interaction. A user can also get information in detail such as SVM score, physicochemical properties including hydrophobicity, hydrophilicity, charge, and molecular weight at the website (https://webs.iiitd.edu.in/raghava/coronavir/dd.php).

Comparison with previous studies

Currently, the quest for effective vaccine design against COVID-19 is increasing among research groups. Similar analyses for vaccine designing are being conducted or already reported in various studies. For instance, a report by Ramaiah and Arumugaswami proposed eight CD4 T cell

Table 4. List of Potential Nucleotide-Based Vaccine Adjuvants, Predicted by the VaccineDA for the 10 Proteins from SARS-CoV-2

Protein name	*Sequence*	*SVM score*	*Length*	*Molecular weight*	*Tm*	*GC content (%)*
Orf8	GCGTTGTTCGTTCTATGAAGACTTTTTAGA	1.885	30	9233.09	57.52	36.67
Orf1ab	ACGTTAATACGTTTTCATCAACTTTTAACG	1.537	30	9130.04	54.79	30
Envelope protein	ACGTTAATAGTTAATAGCGTACTTCTTTTT	1.492	30	9176.08	53.42	26.67
Orf6	ATTATGAGGACTTTTAAAGTTTCCATTTGG	1.33	30	9241.12	54.79	30
Surface glycoprotein	ACTAATGTCTATGCAGATTCATTTGTAATT	1.265	30	9185.09	53.42	26.67
Orf3a	TTCTCTATCTTTATGCTTTAGTCTACTTCT	1.248	30	9044.96	54.79	30
Nucleocapsid glycoprotein	GCGTTGTTCGTTCTATGAAGACTTTTTAGA	1.085	30	9246.08	61.62	46.67
Membrane glycoprotein	TAACTTTAGCTTGTTTTGTGCTTGCTGCTG	1.068	30	9191.04	58.89	40
Orf7a	CTCTAGCTGATAACAAATTTGCACTGACTT	0.797	30	9140.03	57.52	36.67
Orf10	AACGTTTTCGCTTTTCCGTTTACGATATAT	0.796	30	9128.02	56.15	33.33

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SVM, support vector machine.

epitopes in the S, E, M, and N proteins based on the Asia and Asia-Pacific Region population using the computational approach.[69] These epitopes can be recognized by human leukocyte antigen (HLA) isotype DR alleles. Besides, recently Ahmed et al. also suggested potential vaccine candidates, that is, a set of B cell and T cell epitopes derived from S and N proteins for SARS-CoV-2 based on the analysis of experimentally validated epitopes of SARS-CoV having sequence similarity with SARS-CoV-2.[70]

Furthermore, Prachar et al. proposed 174 SARS-CoV-2 epitopes that are *in vitro* validated to bind stably to 11 HLA allotypes , that is, 10 HLA class I and one HLA class II, based on using the computational and *in vitro* analysis.[71] Furthermore, various studies predicted multiepitopes or numerous vaccine candidates for SARS-CoV-2 infections using the computational approach as represented by different preprints.[72–76] The question, why another study for designing an epitope-based vaccine against COVID-19, arises. Best to our knowledge, none of the existing studies identifies epitopes that can activate both innate and adaptive immune systems. In our study, we identified peptides that can activate both arms of the immune system as well as identify promiscuous MHC binders and vaccine adjuvants. As given in Table 2, potential peptides identified in this study have almost all the required properties for an effective vaccine. Besides, the top five vaccine candidates from our study also mapped on six SARS-CoV-2 strains from different parts of the world. This indicates their universal utility aspect. Thus, additional features of our vaccine module will complement existing studies in fighting against COVID-19.

Knowing the fact of the importance of drugs in curbing the COVID-19, numerous researchers focused on the elucidation of potent drugs. In this study, we compile these studies to provide information from a single source. Various reports suggested repurposing of different drugs for COVID-19 patients.[63,77,78] A molecular docking study by Elfiky suggested ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir as potent drugs against SARS-CoV-2 as tightly bound to its RdRP.[79] Moreover, this study also proposed the IDX-184, setrobuvir, and YAK as antiviral treatments for COVID-19.

Furthermore, an *in vitro* study by Wang et al. showed the effectiveness of remdesivir and chloroquine in controlling the COVID-19 infection.[80] Importantly, a study by Chu et al. on 41 patients with COVID-19 who were treated with a combination of lopinavir/ritonavir and ribavirin showed favorable outcomes in comparison with the 111 patients treated with ribavirin only and placebo controls, thus suggesting clinical utility.[65] Moreover, one of the studies is focused on

Table 5. List of the Top 10 OligoNucleotide Candidates That Could Serve as Efficient siRNA Against COVID-19

Protein name	*Antisense sequences of siRNA*	*Position on mRNA*	*mRNA target sequence*	*Target accessibility*	*Efficacy*
Orf1ab protein	AAAUUGAUCGUACAACACG	12	CGUGUUGUACGAUCAAUUU	0.637	1.129
Orf3a protein	AACAACAACAGCAAGUUGC	11	GCAACUUGCUGUUGUUGUU	0.979	1.080
Surface protein	UAAGAUUAACACACUGACU	3	AGUCAGUGUGUUAAUCUUA	0.722	1.078
Envelope protein	UUAACUAUUAACGUACCUG	10	CAGGUACGUUAAUAGUUAA	0.768	1.053
Orf6 protein	UUUAUUCUCAGUUAGUGAC	12	GUCACUAACUGAGAAUAAA	0.654	1.034
Nucleocapsid protein	UUUGUAUGCGUCAAUAUGC	8	GCAUAUUGACGCAUACAAA	0.676	1.033
Membrane protein	AAACAAGCUAAAGUUACUG	3	CAGUAACUUUAGCUUGUUU	0.673	1.010
Orf10 protein	UAACUACAUCUACUUGUGC	4	GCACAAGUAGAUGUAGUUA	0.723	0.981
Orf8 protein	UGAUACUCUAAAAAGUCUU	3	AAGACUUUUUAGAGUAUCA	0.947	0.923
Orf7a protein	AAAUUGAGUGCUAAAGCAA	11	UUGCUUUAGCACUCAAUUU	0.791	0.819

Table 6. List of Potential Drugs That Could Be Used for Treating COVID-19 Infection

S. no.	Drug	FDA-status	SARS-CoV-2 receptors	Targets in DrugBank (PDB ID)	Patchdock score	
					SARS-CoV-2	Targets in DrugBank
1	GS-6620	Investigational	RDRP	Hepatitis C virus Ns5b RNA-dependent RNA polymerase (1C2P)	8724	7364
2	Cobicistat	Approved	3C-like proteinase	NA	8096	NA
3	Ritonavir	Approved, investigational	3C-like proteinase	HIV-1 protease (5V4Y)	7802	8016
4	Remdesivir	Investigational	RDRP	RNA-directed RNA polymerase L (NA)	7554	NA
5	Lopinavir	Approved	3C-like proteinase	HIV-1 protease (5V4Y)	7512	7894
6	Camostat myselate	Experimental	TMPRSS2	NA	6396	NA
7	Darunavir	Approved	3C-like proteinase	HIV-1 protease (5V4Y)	5934	7316
8	Fosamprenavir	Approved	3C-like proteinase	HIV-1 protease (5V4Y)	5934	6754

NA, not applicable; RDRP, RNA-dependent RNA polymerase.

the development of the COVID-19 docking server.[81] This tool predicts the binding modes between COVID-19 targets and the ligands, including small molecules, peptide, and antibody. Besides, Dong et al. summarize the antiviral drugs and their efficacy are included in the guidelines (version 6) for treatment of COVID-19.[27] Inconclusively, all these reports targeted one or other aspect of the various drugs in combating the COVID-19.

In our study, we have tried to cover the holistic view of the drug design or available drugs to curb the COVID-19. Therefore, we have predicted drug targets, their structure, and compiled possible drug molecules from the literature. Besides, to understand host–virus interaction, we have also predicted CPP from viral proteins. One of our goals is the feasibility of identified candidates for the experimental validation. Therefore, we prioritized these vaccine or drug candidates as a minimum manageable subset. Eventually, it will facilitate the possibility of their implementation in real life. To provide complete and comprehensive information, we also compile information from the literature and other Internet resources such as NCBI, WHO, and DrugBank. To facilitate the scientific community against this deadly COVID-19, we provide a web-based platform named CoronaVIR.

Discussion and Conclusion

The ongoing severe pandemic outbreak of COVID-19 is the major concern across the globe. Currently, COVID-19 has affected 215 countries and territories with one international conveyance, that is, the Diamond Princess cruise ship harbored in Yokohama, Japan, as of September 11, 2020 (https://www.worldometers.info/coronavirus/). The containment of COVID-19 and the management of patients are the need of the hour. To tackle this medical emergency, numerous scientists are extensively working on the characterization of SARS-CoV-2 for accurate diagnosis and designing the appropriate vaccines and therapies to cure COVID-19 patients. In addition, various organizations are also actively involved in generating vital statistics and information about the COVID-19 outbreak. This generates plenty of data or information in the form of widely spread literature, resources, videos, etc. One of the major challenges is to manage/accumulate this information at a single platform in a user-friendly manner, to make it approachable to the wider audience such as the scientific community and clinicians for the containment of COVID-19 patients. Since the delay in diagnosis and the lack of effective drugs and vaccines for COVID-19 result in increasing the mortality rate day by day,[82] there is a need to accelerate research in the development of adequate vaccines and drugs. Hence, this study is an attempt to compile this widespread information associated with SARS-CoV-2 or COVID-19 at a single user-friendly web-based platform named ''CoronaVIR'' (https://webs.iiitd.edu.in/raghava/coronavir/), along with predicted novel potential diagnostic, vaccine, and drug candidates based on literature and bioinformatics analysis.

In the CoronaVIR, we have integrated mainly four modules that include ''Genomics,'' ''Diagnosis,'' ''Immunotherapy,'' and ''Drug Designing.'' The ''Genomics'' module provides 53 whole-genome sequences from various countries and sequences of 10 proteins, etc. This will facilitate the users/researchers for the genomic analysis of SARS-CoV-2 to scrutinize vital information of structural and functional components, eventually to design vaccine, drug molecules. The ''Diagnosis'' module provides detailed information regarding currently-in-use diagnostic tests. In addition, we have predicted five novel universal primer candidate sets for the diagnosis of COVID-19 based on 53 genomic sequences of SARS-CoV-2 strains from different parts of the globe. These diagnostic primers need experimental validation as they are designed by *in silico* analysis only. Furthermore, the ''Immunotherapy'' module maintains various peptide and RNA-based immunotherapeutic candidates for COVID-19. In this study, we have proposed 17 potential vaccine candidates that can activate the immune system based on our bioinformatics analysis. Importantly, five peptide sequences, that is, LQLPQGTTLPKGFYA, VILLNKHIDAYKTFPPTE PKKDKKKK, EITVATSRTLS, GKGQQQQGQTV, and SELVIGAVILR, are predicted by most of the immunoinformatics tool such as LBtope, CTLPred, VaxinPAD, ProPred, and Propred 1 and also reported in IEDB. This analysis indicates that these epitopes have the potential of B cell, T cell

activation with MHC binding, and vaccine adjuvant capability; eventually they can activate almost all the arms of our immune system. Furthermore, these five vaccine candidates are also mapped on six SARS-CoV-2 strains from different parts of the globe. This reveals their utility in universal aspects. Besides peptide-based vaccine candidates, we have also discovered siRNA-based therapeutics and nucleotide-based vaccine adjuvants for COVID-19 using the *in silico* approach. Eventually, experimental researchers can further explore these potential vaccine candidates to confirm their clinical utility. Apart from that, drugs are the key means to combat this global disaster of COVID-19. Hence, the ''Drug Designing'' module is integrated to manage information of nine potential drug targets, their structures, number of drug molecules, and drug delivery peptide-based vehicles (CPP). Recently, Wang et al. have shown in their study that a human monoclonal antibody 47D11 binds to SARS-CoV-2 and SARS-CoV and potently inhibits the virus's infection of Vero cells,[83] which suggests that monoclonal antibodies can act as therapeutics to treat COVID-19 patients, although clinical validation is still needed to confirm their potential application in combating COVID-19.

Taken together, CoronaVIR is a comprehensive web-based platform, which accommodates widely scattered information of different aspects, that is, genomics, diagnosis, and therapeutics of the SARS-CoV-2 in a user-friendly manner. We anticipate this would facilitate the researchers involved in managing the COVID-19. Moreover, the novel suggested potential diagnostic, vaccine, and therapeutic candidates based on *in silico* analysis might further help in designing effective diagnostic tools and vaccines for COVID-19, and hence eventually help in combating this COVID-19 medical disaster.

Limitation of the study

The major limitation of the study is that we have not incorporated the recently updated information. The research shows the analysis of the data taken till March 2020. As of now, a huge amount of genomics, proteomics, and therapeutic data are available on NCBI and other resources. Therefore, diagnostic and vaccine candidates designed in this study are derived from the limited amount of information that was available at that time. But we are constantly updating the recent information on our website under various sections (https://webs.iiitd.edu.in/raghava/coronavir/index.html).

Authors' Contributions

S.P., D.K., H.K., N.S., A.D., and S.S. collected the data and processed the data sets. S.P., H.K., D.K., N.S., A.D., S.S., P.A., C.A., and L.M. analyzed and predicted candidates. D.K. and H.K. developed the Genomics module. H.K. and L.M. developed the Diagnosis module. S.P., N.S., A.D., and D.K. developed an Immunotherapy module. S.P., S.S., and P.A. designated the Drug Designing module. S.P., D.K., H.K., N.S., A.D., P.A., C.A., and G.P.S.R created the back-end server and front-end user interface. S.P., H.K., D.K., N.S., A.D., P.A., L.M., and G.P.S.R. analyzed the results. S.P. H.K., D.K., C.A., N.S., and G.P.S.R penned the article. G.P.S.R. conceived and coordinated the project, facilitated in the interpretation and data analysis, and gave overall supervision to the project. All authors have read and approved the final article.

Author Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Table S1
Supplementary Table S2

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