Deciphering the interactions of SARS-CoV-2 proteins with human ion channels using machine learning-based method

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Deciphering the interactions of SARS-CoV-2 proteins with human ion channels using machine learning-based method

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the worldwide COVID-19 pandemic which began in 2019. It has a high transmission rate and pathogenicity leading to health emergencies and economic crisis. Recent studies pertaining to the understanding of the molecular pathogenesis of SARS-CoV-2 infection exhibited the indispensable role of ion channels in viral infection inside the host. Moreover, machine learning-based algorithms are providing higher accuracy for host-SARS-CoV-2 protein-protein interactions (PPIs). In this study, predictions of PPIs of SARS-CoV-2 proteins with human ion channels (HICs) were performed using PPI-MetaGO algorithm. The PPIs were predicted with 82.71% accuracy, 84.09% precision, 84.09% sensitivity, 0.89 AUC-ROC, 65.17% MCC score and 84.09% F1 score. Thereafter, PPI networks of SARS-CoV-2 proteins with HICs were generated. Furthermore, biological pathway analysis of HICs interacting with SARS-CoV-2 proteins showed the involvement of six pathways, namely inflammatory mediator regulation of TRP channels, insulin secretion, renin secretion, gap junction, taste transduction and apelin signaling pathway. The inositol 1,4,5-trisphosphate receptor 1 (ITPR1) and transient receptor potential cation channel subfamily A member 1 (TRPA1) were identified as potential target proteins. Various FDA approved drugs interacting with ITPR1 and TRPA1 are also available. It is anticipated that targeting ITPR1 and TRPA1 may provide a better therapeutic management of infection caused by SARS-CoV-2. The study also reinforces the drug repurposing approach for the development of host directed antiviral drugs.

Key words: virus and host**,** protein interaction networks, cellular pathways, antiviral compounds

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the reason for the ongoing pandemic which started in 2019. It rapidly spread to more than 175 countries within the first three months (1). As of May 2021, more than 159 million confirmed cases have been reported with 3.32 million deaths worldwide (2). The dearth of approved treatment therapeutic strategies specific for SARS-CoV-2 infection impeded disease containment measures and control of the spread of infection. Viruses with small-sized genomes in particular, depend on the host genomic machinery for many of their essential functions via interacting with membrane proteins and regulating HICs (3). HICs are transmembrane proteins which allow the passive flow of ions in and out of cells and cellular organelles owing to their electrochemical gradient. Because of the exchange of ions across the membrane which results in electrical currents, ion channels serve a diverse set of roles in generating membrane potential and cellular activities such as, signal transduction, synaptic release of neurotransmitters, hormone release, muscle activity, cell volume regulation motility, and apoptosis (4). Dysfunction of HICs leads to a class of diseases called channelopathies (4). Numerous viral infections are involved in neuronal pathologies, diarrhoea, cardiomyopathies, bronchitis and pain disorders exploiting a variety of HICs (3).

Studies have shown that Ebola and influenza viruses exploit HICs to enter the host by utilizing Ca^{2+} channels for viral entry (5, 6). Activation of host potassium channels during the first six hours of viral infection by Bunyamwera virus has been shown (7). Also, the use of L-type voltage gated Ca^{2+} channel inhibitor verapamil in the treatment of infection by Filoviruses implicates the importance of HICs in viral survival (7). Deregulation of potassium channels may result in congenital hyperinsulinism and some rare forms of diabetes (8). It can be said that in order to survive and replicate inside a host, viruses must exploit the cellular environment which is highly dependent on the flow of ions into and out of the cell. HICs play a crucial role in viral infection by providing an entry point, supporting viral life cycle and disease progression (9). SARS-CoV-2 enters the host by the process of endocytosis and exploits HICs by elevating cytosolic calcium concentration which further aids in viral replication by inhibiting host protein trafficking and maturation of viral proteins (10-12).

In view of the host-viral interactions for viral replication there are many host factors that could be potential antiviral targets. Thus, HICs interacting with viral proteins are likely to be more effective antiviral targets. Moreover, the development of HIC-viral interactions has provided an insight that channelopathies may explain some commonly observed virus induced

pathologies (3). At present 13% of the clinically approved drugs are ion channel modulators, presenting the hypothesis that ion channels targets could give promising pharmacological results for the alteration of the viral life cycle (7). Systematic mapping of PPIs of SARS-CoV-2 and human proteins has been studied by Gordon *et al.* for exploring host dependencies of the SARS-CoV-2 virus (9). This study has reported various SARS-CoV-2 proteins that interact with several human proteins while many other potential interactions remain to be studied. Host-viral PPIs studied using machine learning (ML) based algorithms lays the foundation for various biological processes including viral life cycles, involvement in host cellular pathways and immune responses against viruses (13). Furthermore, ML algorithms provide the confidence in predicted interactions to improve efficacy of wet lab experiments for drug designing (14). PPIs between SARS-CoV-2 proteins and human proteins implementing ML approaches have been reported (15-17).

In the current study, ML-based algorithms have been applied for the prediction of PPIs between SARS-CoV-2 proteins and HICs. Protein-protein interaction maps (PPIMs) and protein-protein interaction networks (PPINs) have been constructed to understand the role of PPIs in the diseased state. PPINs are being widely used in a number of biological data analyses including pathway analyses, functional annotations and identification of cross talk among the cellular components (18). Biological pathways exploited by HICs as interactors of SARS-CoV-2 have been explored and the putative biological significance of these interactions has been provided. Most likely, this study may unravel the development of future therapeutic strategies against SARS-CoV-2 infection and also aid in repurposing existing drugs.

2. Prediction of interactions between SARS-CoV-2 proteins and HICs using PPI-MetaGO

To predict the PPIs between SARS-CoV-2 proteins and HICs a ML-based approach was used. An overview of the methodology followed to study the PPIs between SARS-CoV-2 and HICs is described in Figure 1.

2.1 Data collection

One of the most crucial steps while building any model based on a ML algorithm is the extraction and enhancement of a good dataset. Primarily, a list of 28 unique SARS-CoV-2 proteins encoding genes were downloaded from the RefSeq database and 328 HIC genes were retrieved from the HGNC database (19). Interactions between HICs and SARS-CoV-2 proteins were parsed from the BioGRID database (release 4.92.192). Dataset included 181 interactions of HICs with SARS-CoV-2 proteins (Supplementary Table 1) and 21 interactions among

SARS-CoV-2 proteins (Supplementary Table 2). The positive dataset consists of 202 interactions which were used as input for PPI-MetaGO. PPIs of SARS-CoV-2 proteins with HICs are depicted as a network (Supplementary Figure 1). As it cannot be proved that two proteins cannot interact, there is no 'gold standard' negative dataset available. Therefore, in PPI prediction tasks, it is common to choose protein pairs uniformly at random from the set of protein pairs that are not known to interact, and treat them as negative dataset (20). For the negative set, first the complement graph of the positive interactions was made and random interactions were taken to form the negative set. Also, the sequences of the proteins were parsed from RefSeq database and gene ontology terms for SARS-CoV-2 proteins were downloaded from Gene Ontology knowledgebase (21, 22).

2.2 Feature extraction

PPI-MetaGO algorithm (23) was applied for the extraction of features of the protein pairs. It is an ensemble supervised meta learner algorithm for PPI prediction. The feature vectors consisting of physicochemical properties of proteins were extracted using sequences of the desired proteins and semantic similarities were extracted using the provided GO terms (23).

2.3 Stacked generalisation method for prediction

Dataset was split into training and testing set of 80:20 ratios. Thereafter, protein sequences and the GO terms were provided as input to the PPI-MetaGO program for the calculation of features and prediction model building. Customized python scripts were used for the generation of input for PPI-MetaGO. PPI-MetaGO uses a stacked generalisation method that allows combining multiple ML algorithms to maximise accuracy. Usage of a single ML-based method may lead to overfitting or underfitting of data even when the parameters are optimised maximally. Bagging and boosting which allow multiple ML-based algorithms only permit combining algorithms of the same type and focus on reducing the variance from multiple classifiers (23). Stacked generalisation uses a meta-ML model which allows combination of different algorithms and aims to reduce the bias of the base generalisers (24). ML-based methods utilized by PPI-MetaGO include random forest, artificial neural network, Naïve Bayes, K-nearest neighbors and support vector machine.

2.4 Evaluation

The PPIs were evaluated using the following performance measures:

$$\text{Accuracy} = \frac{TP+TN}{TP+TN+FP+FN}$$

$$\text{Precision} = \frac{TP}{TP+FP}$$

$$\text{F}-\text{score} = \frac{2\ X\ TPR\ X\ Precision}{TPR+Precision}$$

$$\text{MCC} = \frac{TP\ X\ TN-FP\ X\ FN}{\sqrt{(TP+FP)(TP+FN)(TN+FP)(TN+FN)}}$$

$$\text{Sensitivity} = \frac{TP}{TP+FN}$$

$$\text{False Positive Rate} = \frac{FP}{FP+TN}$$

where TPR, TP, TN, FP, and FN represent true positive rate, true positive, true negative, false positive, and false negative, respectively. In addition, PPI-MetaGO also calculates area under the curve (AUC). AUC is the probability that a random positive sample will have a higher score than a random negative sample. The closer the AUC for a model comes to 1, the better it is. So, models with higher AUCs are preferred over those with lower AUCs. Accuracy of 84.09% and AUC of 0.89 was obtained for SARS-CoV-2 and HIC interactions (Table 1). Confusion matrix obtained for the dataset represents 37 true positives, 7 false positives, 7 false negatives, and 30 true negatives (Table 2).

3. Protein-protein interactions of SARS-CoV-2 proteins with HICs

Functions of HICs interacting with SARS-CoV-2 proteins are provided in Supplementary Table 3. Inositol 1,4,5-trisphosphate receptor type 1 (ITPR1), inositol 1,4,5-trisphosphate receptor type 2 (ITPR2) and Inositol 1,4,5-trisphosphate receptor type 3 (ITPR3) receptors were found to be involved in release of calcium from endoplasmic reticulum (25-28). ANO5, ANO6, ANO8, ANO10 belonging to anoctamin family that are calcium dependent channel proteins (29-35) may be accountable for entry of viral proteins into the cells due to its presence in the transmembrane regions. In the set of 40 proteins, also identified were a bunch of leucine rich volume regulated anion channels which are responsible for various functions like B cell development, maintenance of constant cell volume, efflux of amino acids and import of antibiotic blasticidin-S into the cell (36-41). The potassium voltage gated channels found in the set of the proteins are known to act as modulators of potassium flow into the cell and also have a role in reactivation of naïve T-cells (42-53). A few of the proteins belonged to the transient receptor potential cation channel family which are known to have a role in signal transduction (54-56). The TRPM7 is both an ion channel as well as serine/threonine protein kinase (57). The proteins belonging to voltage dependent anion channels play a role in involving Ca^{2+} ions during viral entry (6, 58, 59). Another important voltage gated channel showing interaction with the

viral proteins were the chloride voltage gated channels which help in maintaining homeostasis and also contributes to acidification thus maintaining lysosomal pH (60-64).

Gap junction proteins may be involved in the cell to cell spread of the virus. Gap junction protein alpha 1 (GJA1) is a component of gap junctions which enables communication between adjacent cells. It was found to interact with M, nsp4, nsp6, ORF7a, ORF7b viral proteins. Viruses destroy cell junctions to invade the host (65). Also, another role of gap junctions reported in viral infection, is the amplification of antiviral signaling in neighbouring cells. It has been studied *in vivo* in influenza virus that STING dependent recognition is essential for limiting virus replication (66). Thus, it can be inferred that gap junctions can act as a port of entry for the virus and may limit the immune reaction against SARS-CoV-2 infection (67). Also, gap junction proteins play major role in contraction of the heart (68-70). One of the unique HICs found to be interacting was the acid sensing ion channel protein (ASIC1) which is usually involved in learning, pain, sensation, memory and fear (71). PKD2, TPCN1, HCN2, SCN9A, GRID1, CHRNA5 and MCOLN3. These proteins function as calcium permeable cation channel, voltage-gated calcium channels across lysosomal membranes, native pacemaker currents in heart, sodium selective channels allowing Na+ to pass according to electrochemical gradient, channels at synapses and cation channels for inwardly rectifying activity respectively (72-78). The glycine receptor beta protein is a part of ligand gated chloride channels (79) and the GABRA5 is a component for heteropentameric receptor for GABA. It may be involved in GABA-A receptor assembly (80).

3.1 PPIs maps of HICs-SARS-CoV-2 proteins

Predicted PPIs maps of HICs-SARS-CoV-2 proteins (Figure 2) were visualized using Cytoscape-3.8 (81). E, M, ORF7b, ORF7a and nsp4 (Figure 2 - i, iii, iv, vii and ix) were found to be interacting with ITPR1, ITPR2 and ITPR3. Nsp6 and ORF8 (Figure 2 - viii and x) were identified to be interacting with ITPR2 and ITPR3. Also, S and ORF6 (Figure 2 - ii and vi) interacted with ITPR3. Viruses exploiting ITPRs is reported to affect the host by increasing metabolic stress and enterotoxicity (82). Moreover, it has also been reported that viral infection promotes depletion of endoplasmic reticulum (ER) Ca^{2+} storage using ITPRs that in turn promotes viral replication (82). Interaction of SARS-CoV-2 proteins with ITPRs may promote viral replication inside the host cells.

E, M, ORF7b, ORF3a, ORF7a, nsp6, nsp4 and ORF8 proteins (Figure 2 - i, iii, iv, v, vii, viii, ix and x) were found to be interacting with leucine rich repeat containing 8 VRAC subunit A (LRRC8A). LRRC8A play an important role in T-cell/ B-cell development. It also plays a role in development and function of lymphocytes (66). Thus, it could be expected that interaction between LRRC8A and SARS-CoV-2 proteins may play a role in impairment of T-cell development during the course of disease pathogenesis.

M, ORF3a, nsp6 and nsp4 (Figure 2 – iii, v, viii and ix) were found to be interacting with voltage dependent anion channels VDAC2 and VDAC3 and E, ORF7b, ORF6, ORF7a, nsp14, nsp5 and nsp13 (Figure 2 - i, iv, vi, vii, xii, xiii, xiv) were found to be interacting with VDAC3. Voltage dependent anion channels (VDACs) present in outer membrane of mitochondria and found to be involved in transportation of metabolites from mitochondria to ER during viral replication while interacting with structural and non-structural proteins of dengue virus (59).

It is known that the coronavirus family uses E protein to induce intracellular membrane remodelling generating new membrane vesicles which serves as a viral replication site. They are responsible for depolarisation of membranes. Furthermore, E protein helps in budding and release of virus particles. Also, the M protein is a transmembrane glycoprotein which along with E protein is responsible for the determination of virion assembly (83). The nsp3, nsp4 and nsp6 interacting with the HICs have also been found to contain a transmembrane domain. These nsps are involved in host membrane remodelling and are known to act as membrane anchors for replication and transcription complexes (84, 85). This sheds light on the fact that these viral proteins have similar properties and may be invading the host by mimicking the ion channels present in the host. This can as well be attributed to the presence of a signature sequence in the Chlorella virus PBCV-1 Kcv viroporin showing architectural similarity with eukaryotic Kir channels (86). Hence it is important to understand the function of viroporins in the manipulation of host-specific processes. However, targeting them can be a challenge due to resistance polymorphism exhibited by viruses.

3.2 The protein-protein interaction networks (PPINs) of HICs-SARS-CoV-2 proteins

PPIs of 40 HICs interacting with SARS-CoV-2 proteins were generated using STRING database (v11) (87). Furthermore, visualization of PPINs of HICs-SARS-CoV-2 proteins were performed using Cytoscape-3.8 (81). PPINs for the SARS-CoV-2 proteins and HICs served in

the identification of major HICs that are common interactors of SARS-CoV-2 proteins S, M, E, ORF3a, ORF6, ORF7a, ORF7b, ORF8, nsp4 and nsp6 (Figure 3).

4. Biological interpretation of HICs-SARS-CoV-2 PPINs

The KEGG PATHWAY analysis of HIC dataset interacting with SARS-CoV-2 proteins was performed using STRING database (v11). Total forty-one biological pathways were identified in which the interacting HICs were involved. Statistical measures including strength and false discovery rate (FDR) score provided by p-values were considered. Six pathways were further studied for the biological interpretation of PPINs (Table 3).

4.1 KEGG PATHWAY analysis of HICs interacting with SARS-CoV-2 proteins

Transient Receptor Potential (TRP) channels that respond to temperature are known as thermo-TRPs. Among the thermo TRPs; TRPA1, TRPM8, TRPV1-4 are found in the nerve endings and plays major role in pain perception and these can be modulated indirectly by inflammatory mediators such as proinflammatory cytokines (88). Activation of TRPV1 increases the release of several pro-inflammatory molecules, including substance P (sP) and cytokines such as, interleukin-6. Respiratory pathophysiology in SARS-CoV-2 infection may show mechanisms related to TRPV1 receptor sensitization resulting in hyper inflammation of the lungs and associated complication (89). Moreover, taste transduction pathway also involves the role of TRPs. It has been observed that as compared to other oral tissues, the salivary gland cells of the tongue and tonsils have the ACE2 receptor and the enzyme TMPRSS that allows the virus to fuse its membrane with that of the host cell and slip inside (90). It would then appear that infection with SARS-CoV-2 in the oral cavity could cause changes in the production or quality of saliva, contributing to the symptoms of loss of taste. TRP channels have a role in the transmission of sensory stimuli of taste (91). Recently it has been reported that TRPA1 are sensitive during the Reactive Oxygen Species (ROS) (92). Particularly TRPA1 is activated by ROS and they may increase the sensitivity to evoke pain and several other symptoms associated with SARS-CoV-2 infection.

Pancreatic beta cells are specialized endocrine cells that continuously sense the blood glucose level and secrete insulin to maintain homeostasis. Glucose-induced insulin secretion is the main principle of insulin release (93). Deterioration in glycemic levels including both insulin resistance and impaired insulin secretion has been recently reported upon SARS-CoV-2 infection (94, 95). Also, a recent study showed that *ACE2* expression is increased considerably

in human pancreatic beta cells in response to inflammatory cytokines thus rendering the beta cells more susceptible to infections (96). Likewise, gap junctions contain the intercellular channels that allow a direct communication between the cellular compartments. These channels permit the direct transfer of ions, amino acids, second messengers and other metabolites between adjacent cells. Change in the intracellular Ca^{2+} levels act as stimuli to the gap junctions. ITPRs (ITPR1, ITPR2, ITPR3) plays a crucial role in maintaining intracellular Ca^{2+} as they act on endoplasmic reticulum for the regulation of cytoplasmic calcium concentration.

The renin-angiotensin-aldosterone system (RAAS) is the essential system for electrolyte homeostasis and blood pressure management through the ACE2 axis. Deregulation of RAAS homeostasis results in development of distress in lungs in terms of triggering inflammation, inducing apoptosis, vasoconstriction, increased oxidative stress and edema (97). ACE2 acts as a port of entry for SARS-CoV-2 virus via interacting with S protein (98). As infection progresses, expression level of ACE2 gets decreased. Reduction in expression level of ACE2 can be correlated to the increase in Ca^{2+} concentration dependent metalloproteinase domain-containing protein (ADAM10). Increase in Ca^{2+} concentration can be attributed to viral proteins interacting with ITPR3 (99). Decrease in ACE2 level leads to accumulation of angiotensin II which further activates angiotensin II type 1 receptor (AT1R) axis thus further worsening the disease outcome. Furthermore, apelin signaling can also be suggested to be involved in disease progression. Apelin peptides are endogenous ligands of G protein coupled receptors APJ. Apelin plays a number of roles in the mammalian system by protecting cardiac health and calcium modulation (100). It has a counter role against ACE2-angiotensin II-AT1R axis activation. Viral proteins interact with IP3R resulting in modulation of Ca^{2+} concentration in cardiomyocytes which further leads to cardiac dysfunction. Because of its counteractive role in ACE2-angiotensin II-AT1R axis and modulation of Ca^{2+}, apelin possesses the potential of alleviating the cardiac and respiratory complications in SARS-CoV-2 infection. ACE-2 downregulation is associated with later stages of COVID-19 infection; hence, apelin administration at this time frame might serve a potential role in reduction of complications associated with SARS-CoV-2 infection. Experimental studies exhibit that apelin administration also has anti-inflammatory effects (101).

4.2 Drugs interacting with potential HICs

HICs interacting with viral proteins can be potential drug targets for drug repurposing. Also, the traditional drug development method is considerably expensive and time consuming. Drug

repurposing is an efficacious process by which effective drugs can be identified. The US food and drug administration (FDA) approved drugs interacting with HICs were identified using DGIdb (102, 103). Table 4 contains the list of HICs including TRPM4, TRPA1 and ITPR1 interacting with FDA approved drugs. Drugs interacting with HICs were overlaid on HICs-SARS-CoV-2 PPINs highlighting potential drug targets (Figure 4). List of drugs interacting HICs and SARS-CoV-2 protein is listed in Supplementary Table 4. Drugs targeted against HICs can be toxic in some cases (104). Furthermore, these drugs can be tested for antiviral activity.

5. Conclusions

Several computational approaches including ML-based algorithms were applied for the prediction of potential target HICs interacting with SARS-CoV-2 proteins. Biological insights of HICs interacting with SARS-CoV-2 proteins were gained using pathway analysis. ITPR1 was found to be involved in four predicted pathways including Inflammatory mediator regulation of TRP channels, gap junction, renin secretion and apelin signaling pathways. TRPA1 can also be a potential target protein as it plays an important role in heat, pain, and taste sensitivity in the host. Moreover, identified FDA approved drugs interacting with potential HICs can be repurposed. Most likely, ITPR1 and TRPA1 can be targeted for better management of infection caused by SARS-CoV-2.

6. Author contributions

JS conceptualized and designed the study. NSM, DS, AG, AP, MB and JS analyzed and interpreted the data. NSM, AG, KTSP, AP, MB and JS contributed to the writing of the manuscript and the figures were prepared by KTSP.

7. Conflict of interests

The authors declare no conflicts of interest.

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Tables

Table 1: Overall Performance of PPI-MetaGO

Accuracy	Precision	F1 Score	AUC-ROC	MCC	Sensitivity	False Positive Rate
82.71	84.09	84.09	0.89	65.17	84.09	18.91

Table 2: Confusion matrix obtained from PPI-MetaGO

	True Positive	True Negative

Predicted Positive	37	7
Predicted Negative	7	30

Table 3: List of KEGG pathways and potential target proteins

KEGG Pathway	**Potential Target Proteins**	**Strength**	**False Discovery Rate**
Inflammatory mediator regulation of TRP channels	ASIC1,TRPA1,ITPR1,ITPR2, ITPR3	1.46	0.0000328
Insulin secretion	TRPM4,KCNN4,KCNJ11, ITPR3	1.4	0.00022
Renin secretion	ITPR1,ITPR3,ITPR2	1.4	0.0012
Gap junction	GJA1,ITPR1,ITPR3,ITPR2	1.39	0.00022
Taste transduction	GABRA5,ITPR3,SCN9A	1.29	0.0017
Apelin signaling pathway	ITPR1,ITPR3,ITPR2	1.08	0.004

Table 4: List of drugs associated with potential target proteins and processes involved

	Drug Name	**Target Protein**	**Biological Processes**
1	Adenosine Diphosphate, Clotrimazole, Adenosine, Spermine, Adenosine Triphosphate, Glyburide	TRPM4	Insulin secretion
2	Thymol, Benzoquinone, Chloropicrin, Allicin, Morphanthridine, Polygodial, Methylglyoxal,Isovelleral, Acrolein, Nicotine, Menthol, Acetaldehyde, Salirasib,	TRPA1	Inflammatory mediator

	Auranofin, Apomorphine, Cannabidivarin, Tetrahydrocannabivarin, Levomenthol, Butamben, Camphor, Cannabidiol, Nabiximols, Phenethylisothiocyanate, Benzyl isothiocyanate, Isopropyl isothiocyanate, Voacangine, Erucin, Allyl isothiocyanate, 4-Hydroxynon-2-enal		regulation of TRP channels
3	Carbenoxolone, Octanol, Carvedilol, Epigalocatechin Gallate, Bleomycin, Propylthiouracil, Labetalol, Atenolol	GJA1	Gap junction
4	Chlorzoxazone, Senicapoc, Clotrimazole, Nitredipine, Riluzole, Quinine, Halothane	KCNN4	Insulin secretion
5	Diminazene, Amiloride, Ibuprofen, Nafamostat, Benzamil	ASIC1	Inflammatory mediator regulation of TRP channels
6	Caffeine, Adenosine Triphosphate, Nitroprusside, Glycerin,	ITPR1	Renin secretion, Apelin signaling pathway

Figure Legends

Figure 1: A schematic overview of several analyses carried out to study the interactome of SARS-CoV-2 proteins with human ion channels.

Figure 2: A depiction of protein-protein interactions of SARS-CoV-2 proteins (i) E (ii) S (iii) M (iv) ORF7b (v) ORF3a (vi) ORF6 (vii) ORF7a (viii) nsp6 (ix) nsp4 (x) ORF8 (xi) nsp3 (xii) nsp14 (xiii) nsp5 (xiv) nsp13 and (xv) nsp16 with human ion channels (HICs). Yellow colour diamond shaped node represents SARS-CoV-2 proteins and HICs are represented as blue colour diamond shaped node.

Figure 3: A schematic representation of protein-protein interaction networks of human-SARS-CoV-2 proteins: proteins-proteins interactions of human ion channels (HICs) were generated using STRING database (purple colour nodes). Furthermore, HICs interaction networks were overlaid with SARS-CoV-2 proteins (i) M, (ii) E, (iii) ORF7a (iv) S, (v) ORF6, (vi) ORF3a, (vii) ORF8, (viii) ORF7b, (ix) nsp6 and (x) nsp4. Yellow colour node represents SARS-CoV-2 proteins and human ion channels are represented in purple colour node.

Figure 4: Representation of human ion channels-drug target network: Significant interactions between SARS-CoV-2 proteins (i) M, (ii) E, (iii) ORF7a, (iv) nsp6, (v) S, (vi) ORF8, (vii) ORF7b and (viii) nsp4 (yellow colour nodes), potential human ion channels (HICs) (blue colour nodes), and FDA approved drugs (black) as identified by DGIdb. HICs-drug interactions were overlaid on protein-protein interaction networks and potential drug-target interactions are presented in the network.

Figures

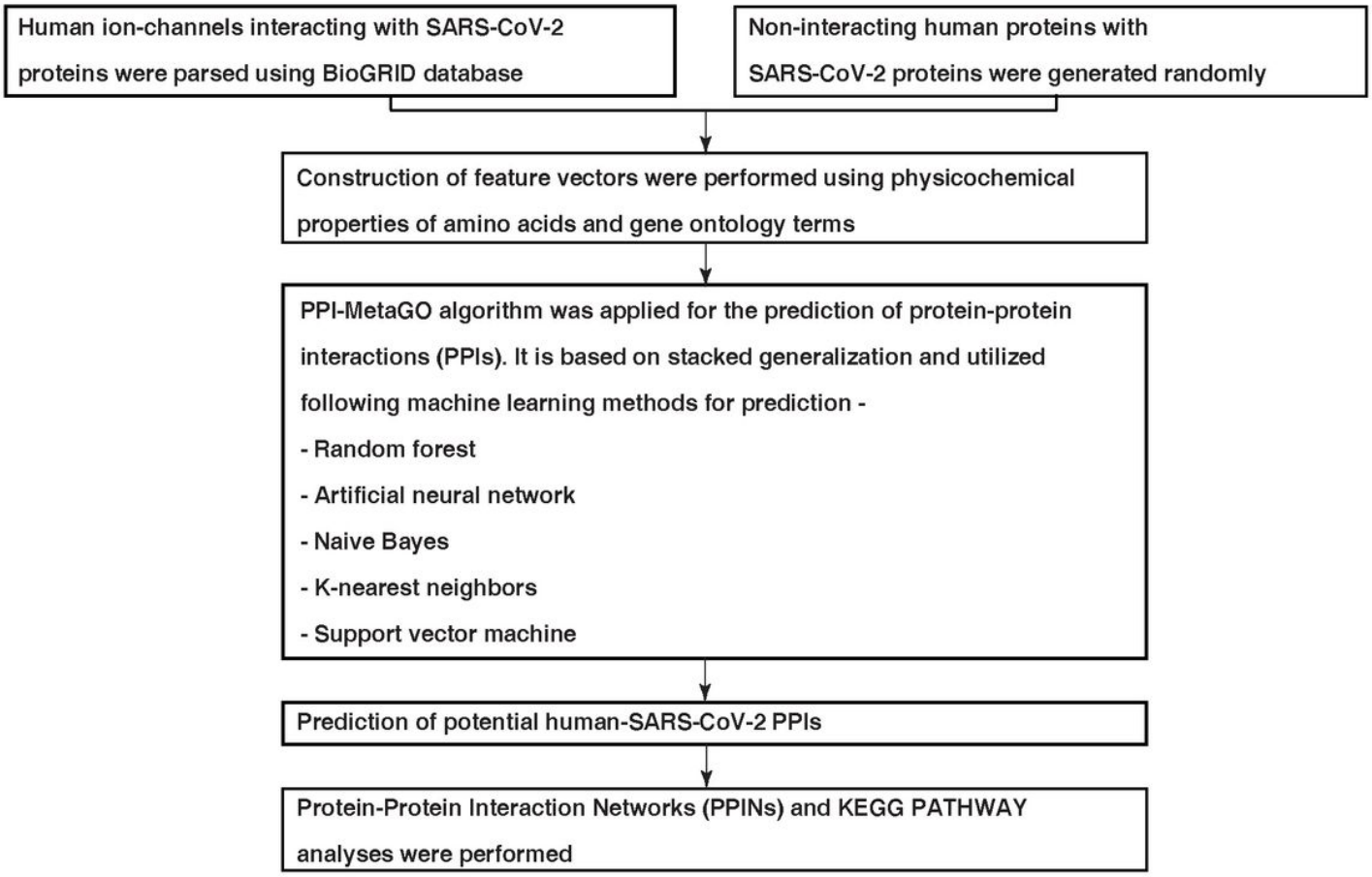
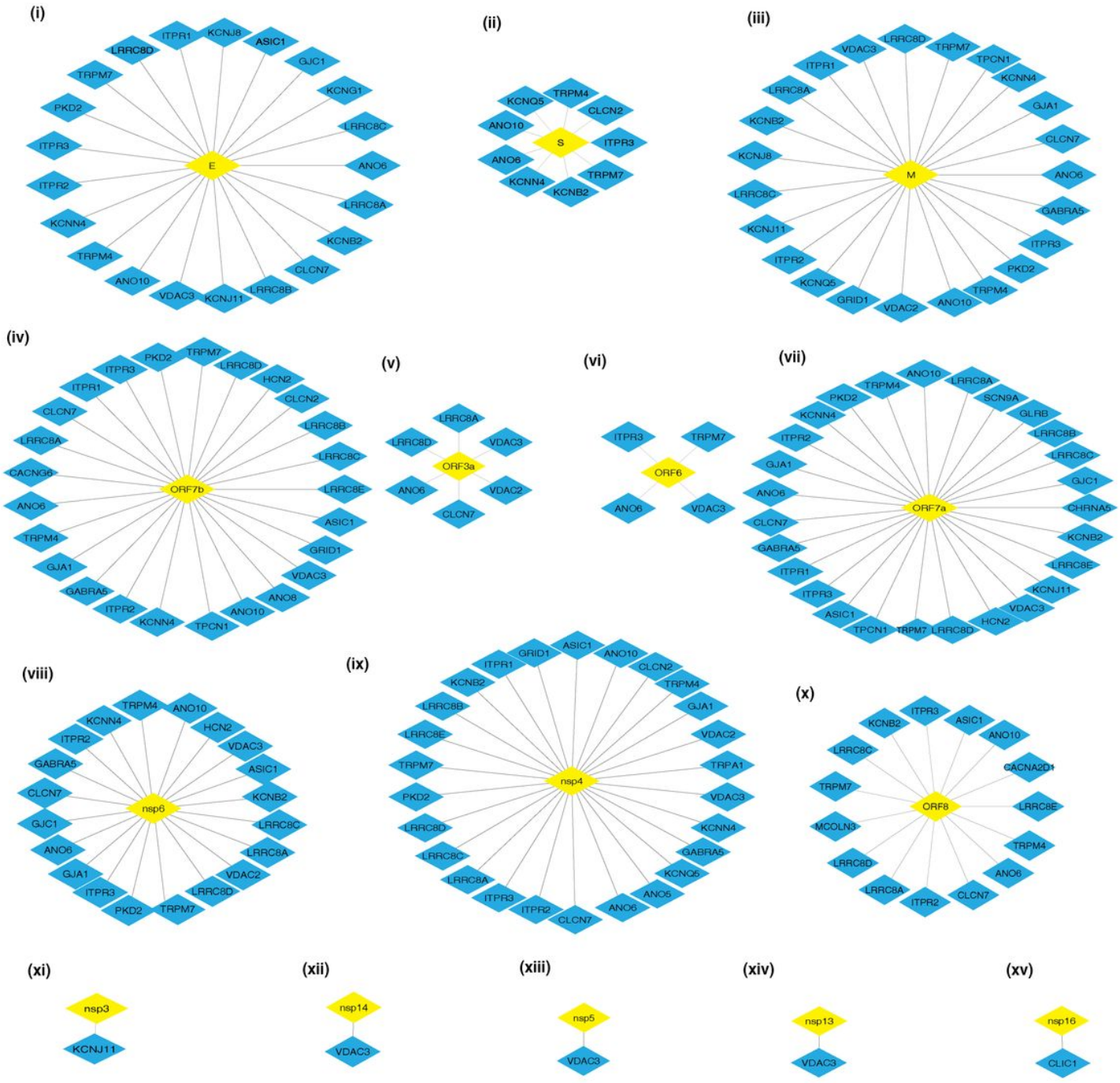


Figure 1

A schematic overview of several analyses carried out to study the interactome of SARS-CoV-2 proteins with human ion channels.



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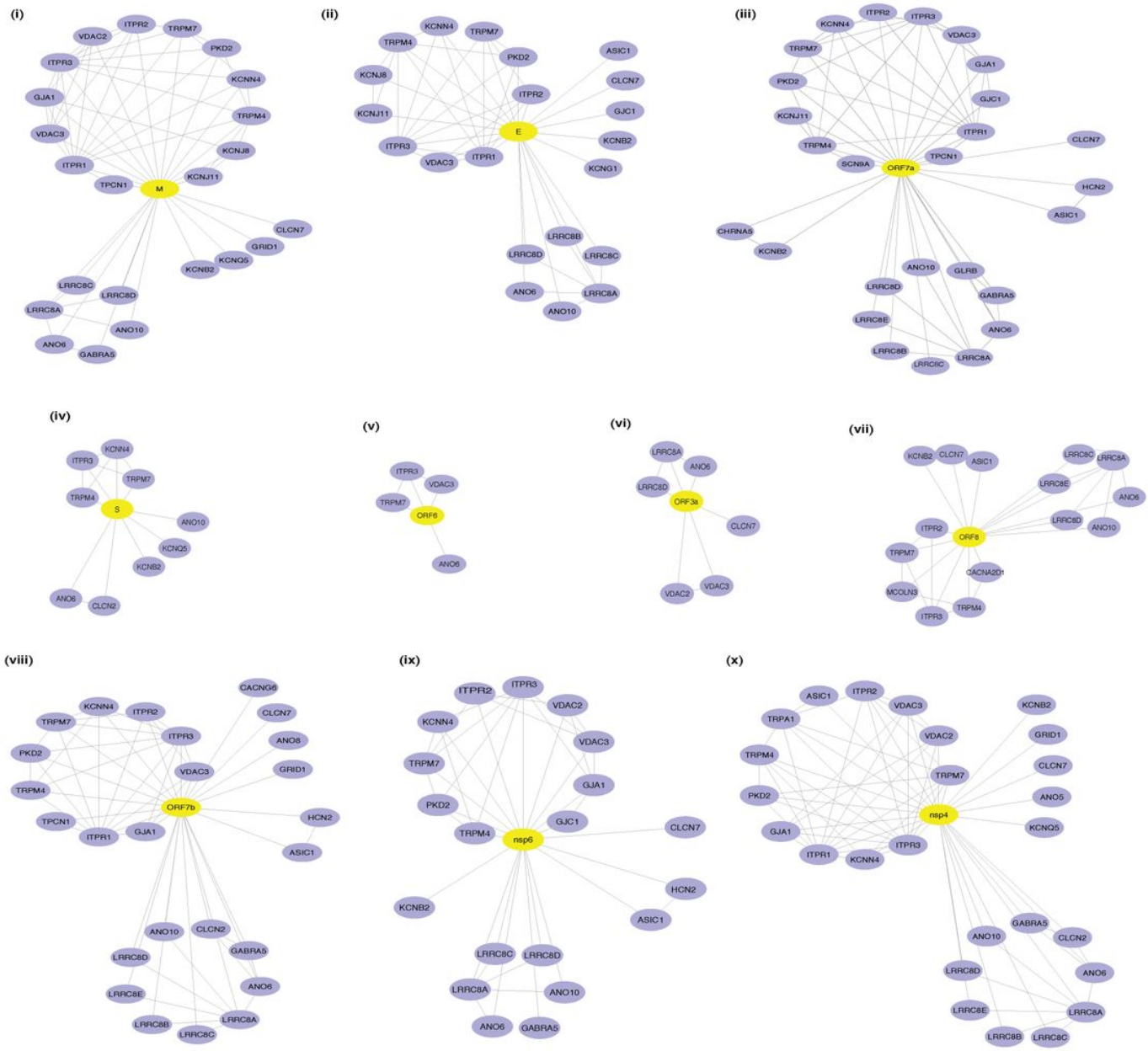

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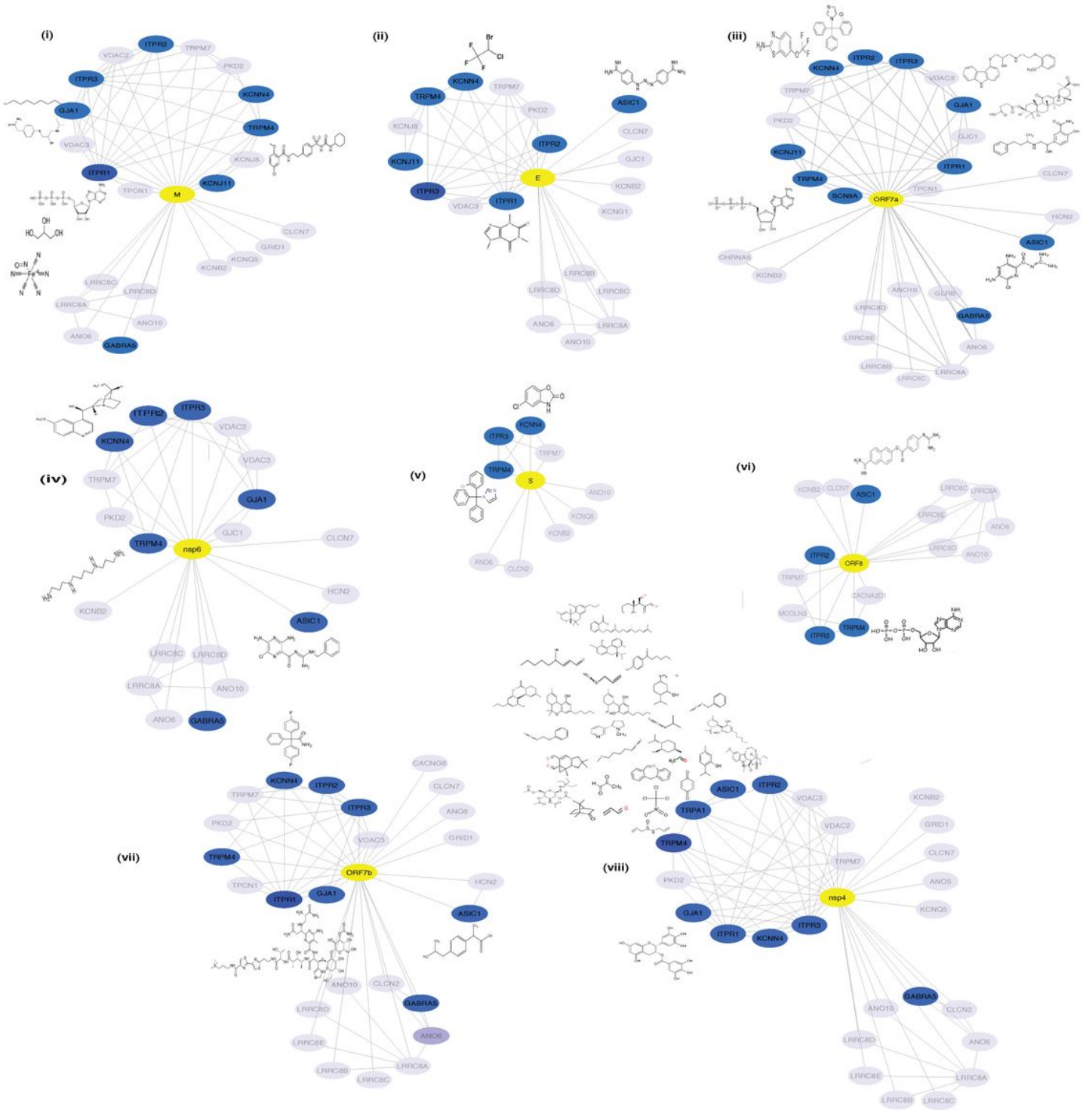

Figure 4

Representation of human ion channels-drug target network: Significant interactions between SARS-CoV-2 proteins (i) M, (ii) E, (iii) ORF7a, (iv) nsp6, (v) S, (vi) ORF8, (vii) ORF7b and (viii) nsp4 (yellow colour nodes), potential human ion channels (HICs) (blue colour nodes), and FDA approved drugs (black) as identified by DGIdb. HICs-drug interactions were overlaid on protein-protein interaction networks and potential drug-target interactions are presented in the network.

Supplementary Files

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