



Original article

In-silico network-based analysis of drugs used against COVID-19: Human well-being study



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ABSTRACT

Introduction: Researchers worldwide with great endeavor searching and repurpose drugs might be potentially useful in fighting newly emerged coronavirus. These drugs show inhibition but also show side effects and complications too. On December 27, 2020, 80,926,235 cases have been reported worldwide. Specifically, in Pakistan, 471,335 has been reported with inconsiderable deaths.

Problem statement: Identification of COVID-19 drugs pathway through drug-gene and gene-gene interaction to find out the most important genes involved in the pathway to deal with the actual cause of side effects beyond the beneficent effects of the drugs.

Methodology: The medicines used to treat COVID-19 are retrieved from the Drug Bank. The drug-gene interaction was performed using the Drug Gene Interaction Database to check the relation between the genes and the drugs. The networks of genes are developed by Gene MANIA, while Cytoscape is used to check the active functional association of the targeted gene. The developed systems cross-validated using the EnrichNet tool and identify drug genes' concerned pathways using Reactome and STRING.

Results: Five drugs Azithromycin, Bevacizumab, CQ, HCQ, and Lopinavir, are retrieved. The drug-gene interaction shows several genes that are targeted by the drug. Gene MANIA interaction network shows the functional association of the genes like co-expression, physical interaction, predicted, genetic interaction, co-localization, and shared protein domains.

Conclusion: Our study suggests the pathways for each drug in which targeted genes and medicines play a crucial role, which will help experts *in-vitro* overcome and deal with the side effects of these drugs, as we find out the *in-silico* gene analysis for the COVID-19 drugs.

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1. Introduction

With great endeavor searching and repurpose drugs, scientists worldwide might be potentially effective in fighting newly emerged coronavirus (Dong et al., 2020). It was one of the leading

pathogens with clinical manifestation with viral pneumonia (Chan et al., 2020; Kumar, 2020; Lu et al., 2020). According to the data compiled by world meter (<https://www.worldometers.info/coronavirus/>) December 27, 2020 estimations, 80,926,235 cases of COVID-19 were reported worldwide. Of these 1,768,844 died and 57,115,759 recovered, but still affected number of patients were 22,041,632 in which 21,936,388 (99.5%) in mild condition while 105,244 (0.5%) in critical condition.

On December 31, 2019, unknown cause pneumonia cases were reported in Wuhan City by the Health Commission of Hubei province, China, with clinical manifestation with viral pneumonia (Chan et al., 2020; Kumar, 2020; Lu et al., 2020; Tahir Ul Qamar et al., 2019; Wu et al., 2020). It was confirmed that the virus belongs to the family coronaviridae subfamily Orthocoronavirinae

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and order nidovirales (Kumar, 2020; Lu et al., 2020). Coronavirus was a non-segmented, enveloped, positive-stranded RNA virus with RNA genome (Chen et al., 2020; Lu et al., 2020; Wu et al., 2020). The common signs and symptoms of coronavirus comprise cough, difficulty in breathing, pyrexia, highly fatal pneumonia, and more critical forms were kidney infections, confusion, diarrhea, rhinorrhea, vomiting, and nausea. Senior citizens were more likely to be affected by this disease (Chen et al., 2020).

Several medicines were in use to fight COVID-19; the major ones include Azithromycin, Bevacizumab, Chloroquine, Hydroxychloroquine, and Lopinavir (Fohner et al., 2017; Gautret et al., 2020; Kini et al., 2019; Pant et al., 2020; Xue et al., 2014)

Azithromycin was a wide-spectrum antimicrobial macrolide antibiotic drug (Fohner et al., 2017). These were widely used for respiratory, intestinal, and infectious conditions (McMullan and Mostaghim, 2015). A study by the French government stated that a combination of Azithromycin and hydroxychloroquine could be taken for SARS-2 because these compounds well tolerate patients, but further evidence studies redemanded (Gautret et al., 2020). Generally, Azithromycin was rigorously permitted, but the side effects recurred include diarrhea, gastrointestinal upset in company with abdominal pain, problems related to the peripheral nervous system (chiefly dizziness or headache, or both of them) furthermore nausea also delineate (Hopkins, 1991; McMullan and Mostaghim, 2015). The adverse effect also varies with the patient's age (Hopkins, 1991).

Bevacizumab was a vascular endothelial growth factor-A-specific angiogenesis inhibitor recombinant humanized monoclonal immunoglobulin (Ig) G1 antibody that binds to every circulating, soluble human vascular endothelial growth factor-A (VEGF), VEGF-A isoforms (Amawi et al., 2020; Garcia et al., 2020; Li and Kroetz, 2018; Rossi et al., 2017). Bevacizumab was relatively easy for both physician management and patient tolerance and may yield more favorable results (Kini et al., 2019). But it can have potentially serious side effects that can lead to serious illness. The most prominent side effects were hypertension (HTN), thromboembolism, proteinuria, and a persistent elevation of arterial blood pressure, which caused a cardiovascular impediment, bleeding, delayed wound healing, and gastrointestinal events (Lu et al., 2020). Rare cases of a hypertensive dilemma with subarachnoid and encephalopathy have been described (Li and Kroetz, 2018). Bevacizumab was undergoing an examination to treat COVID-19 and its outburst, but its administration was limited because of its possible serious complications (Amawi et al., 2020).

Chloroquine was an antimalarial agent (Browning, 2014; Xue et al., 2014). Significant side effects were gastrointestinal distress, nausea, vomiting, diarrhea, abdominal cramps, the outcome of ventricular arrhythmias, hypoglycemia in diabetic patients, and neurotoxicity in tinnitus headaches, mood swings, hemolytic anemia in individuals with G6PD deficiency. In some patients, significant QTc lengthening and cardiac arrhythmias (Gautret et al., 2020). The adverse effects on the hematologic, hepatic, and renal systems (Jean et al., 2020). These drugs may also induce cardiac toxicity, lead to irreversible damage and death (Chatre et al., 2018). Their adverse effects were well known and can range from psychological effects to arrhythmias and sudden death (Moore, 2020).

Hydroxychloroquine and Chloroquine have been documented as potential "game-changers" in the press briefing of COVID-19 (Gautret et al., 2020). Although hydroxychloroquine was less toxic than Chloroquine and well-tolerated. Many complications have been reported, including ocular complications, majorly corneal deposits (Jorge et al., 2018), cardiovascular side effects, skin complications, neurological side effects, liver side effects, gastric or peptic ulcer complications (Ponticelli and Moroni, 2017). Presently, at least 80 trials of Chloroquine, hydroxychloroquine, or both, com-

bined with other drugs, have been recorded globally (Ferner and Aronson, 2020; Ponticelli and Moroni, 2017; Yogasundaram et al., 2014).

For the approved usage of the medicines, the Food and Drug Administration is consistently evaluating the emanate data and published literature (FDA, 2020). On BARDA solicit, March 28, 2020, FDA announced two major therapeutics, CQ and HCQ, to be used on an emergency basis for COVID-19 but on June 15, 2020, FDA rejected its use (FDA, 2020; Infante et al., 2020) But studies were still there which suggest the rational use of the CQ and HCQ for covid-19 patients (Infante et al., 2020). Therefore, both Chloroquine and hydroxychloroquine were also included in the study.

Lopinavir was an antiretroviral protease inhibitor (Cao et al., 2020). Several complications have been reported, like gastrointestinal adverse events, including anorexia, nausea, abdominal discomfort, or diarrhea, as well as two serious adverse events, both severe gastritis (Arabi et al., 2018). Such side effects, including hepatic injury, pancreatitis, more severe cutaneous rupture, and the risks of QT proliferation, and the ability to interact with multiple drugs due to the prohibition of CYP3A, were well documented (Cao et al., 2020). In the medical care of COVID-19, no benefits were observed. But it did show some secondary points of benefits (Cao et al., 2020; Stower, 2020). Arabi et al. (2018) reported significantly lower adverse side effects with a combination of lopinavir used in 41 patients with SARS-2 was associated. Lopinavir has been recommended by the National Health Commission and National Administration of Traditional Chinese Medicine as a therapeutics of COVID-19 (Zhu et al., 2020). Recommended in vitro treatment and antiviral sensitivity tests show that the SARS coronavirus's cytopathic effect was inhibited by it (Chu et al., 2004).

The drug-gene interaction shows how mutated genes can be targeted in therapy, and drug development can be prioritized (Griffith et al., 2013). Databases and tools supply a powerful interface for finding and query gene lists against drug-gene interactions and possible combinations of 'drug-gene' interactions in a single resource (Cotto et al., 2018; Griffith et al., 2013). Gene-gene interactions identify a collection of genes most likely to be a shared function based on their interaction with that gene (Zuberi et al., 2013).

In large-scale functional analysis, it was common to estimate the active association between an experimentally derived gene or protein set and a database of exciting gene/protein sets (Glaab et al., 2012). To this end, the over-representation enrichment analysis was applied over the most widely used method (Glaab et al., 2012). Nevertheless, enrichment provides scores to measure the genes' functional associations (Glaab et al., 2012). The pathway enrichment analysis offers complete biomedical and physiological research (Fabregat et al., 2017).

In this research work, we *in-silico* examine these drugs to check and help experts invitro to eliminate the side effects beyond its beneficial effects. We find out the most critical genes targeted by the drug also its gene-gene interactions were performed. The pathways were also identified along with the verification of gene-identifier mapping necessary to deal with the drug-related complications.

2. Materials and methods

2.1. Selection of disease through literature

The first step was selecting the most threatening virus called SARS-2 through literature that helps us formulating and analyzing the problem statement. The disease was selected based on its severity; it was also the need of time to help overcome and elimi-

nate the drug's complications and side effects (Gandhi et al., 2020) (see Fig. 1).

2.2. Selection of drugs used against COVID-19 from DrugBank

In the second step, the drugs that were used against COVID-19 were retrieved from the DrugBank (<https://www.drugbank.ca/>). DrugBank was an online comprehensive, widely defined, freely available database containing large-scale biochemical and pharmacological information for drugs, their mechanisms, and their targets. Developed, maintained, and improved by extensive literature surveys conducted by domain-specific experts and skilled curators (Law et al., 2014; Wishart et al., 2008, 2018).

2.3. The drug-gene interaction using drug gene interaction database

In the third step, the drug-gene interaction was performed on the selected drugs by using Drug Gene Interaction Database (DGIdb) (<http://www.dgidb.org/>). The Drug Gene Interaction Database (DGIdb) was an open-source software prospect current resources to create assumptions from papers, databases, and web resources (Cotto et al., 2018; Griffith et al., 2013).

2.4. Gene-Gene interaction using GeneMANIA

In the fourth step, a query list of the genes that were obtained from drug-gene interaction was given to GeneMANIA. GeneMANIA tested the weights from data sources based on their predicted value for reestablished the query list. GeneMANIA generates speculation regarding gene function, analyzing gene lists, and prioritizing functional genes for functional evaluation. It then expanded the query list with practically identical genes that had common characteristics with the initial query genes and displayed an interactive, applicable association network, allow the genes to reveal the relationship between datasets (Franz et al., 2018; Montojo et al., 2010; Mostafavi et al., 2008; Vlasblom et al., 2015; Wardle-Farley et al., 2010; Zuberi et al., 2013).

2.5. The development of gene-gene interaction network

In the fifth step, for the precise estimation of the gene-gene interaction network, Cytoscape was used. Cytoscape was a powerful, extreme performance, and positively integrating software for visualizing and interpreting the systems. Cytoscape also allows arbitrary data integration, graphical representation, integrated data, selection and filtering tools, and plugins to implement external methods for a better interface. In this step-through Cytoscape, the duplicated edges were removed, and a proper layout was chosen. Also, for precise analysis, each gene function's contribution, different shapes, and colors were selected (Alberts et al., 2019; Otasek et al., 2019; Shannon et al., 1971).

2.6. Network-based pathway enrichment analysis

For the functional association between the genes, EnrichNet (<http://www.enrichnet.org>) was used in the final step. Enrichment analysis was applied over a set of genes of drug-gene and gene-gene interaction genes obtained through GeneMANIA. The default molecular network STRING Dear Dr. Rajan,

Thank you very much for email. I was stuck in the USA due to travel restrictions. Please accept my apology for the delay in a report of your student.

I will submit my report within four weeks if your Examination department and you agree to grant this extensions used with the ENSEMBL ID identifier format. Reactome was used for pathways and processes for the analysis, visualization, and interpretation of

the query gene list. Network distance distribution (XD-score), the significance of overlap genes (Fisher-test, q-value). Also, gene identifier mapping was done by enrichment analysis (Glaab et al., 2012).

3. Results

Through continuous literature review, we find out that scientists were searching and repurpose drugs which were potentially useful in fighting human coronavirus (Dong et al., 2020). The drugs that were used against the coronavirus disease COVID-19 were retrieved through the DrugBank. DrugBank search engine generates numerous drugs that were used for the treatment of COVID-19. But the five most important drugs were selected for analysis, interpretation, and visualization (Table 1). Azithromycin, Bevacizumab, Chloroquine, Hydroxychloroquine, and Lopinavir as shown in Fig. 2 and also detail in Table 1.

Next, one of the methodology's significant steps was drug-gene interaction through the drug-gene interaction database abbreviated as DGIdb. The results showed that the drug- targeted 9-genes, 37-genes, 9-genes, and 3-genes for Azithromycin, Bevacizumab, Chloroquine, -Hydroxychloroquine, lopinavir, respectively (Table 2).

The gene-gene interaction was done by using GeneMANIA that was a Gene Multiple Association Network Integration Algorithm, a large set of functional association data. GeneMANIA provides an output of 29 genes that were interacted with each other for Azithromycin, 72-genes for Bevacizumab, 25-genes for Chloroquine, 29-genes for hydroxychloroquine, and 23-genes for lopinavir (Figs. 3–7).

Next, for explicit estimation, the duplicated edges for each gene interaction network were removed through Cytoscape. For azithromycin drug gene-gene interaction, 89 duplicate edges, for Bevacizumab 669 identical edges, for chloroquine 97 same edges, for hydroxychloroquine 174 exact edges, and lopinavir 111 very edges were removed, and a proper layout was chosen to give a clear picture of the network. The co-expression, physical interaction, pathway, predicated, genetic exchange, co-localization, shared protein domain, and no definite network group (but present in function) were represented with different shapes for precise analysis of each gene function and color (Figs. 3–7).

In Azithromycin, the output of 29 genes was generated, which interacted with each other. These were involved mainly in cyclic nucleotide biosynthesis process, nucleotide biosynthetic process, purine nucleotide biosynthetic process, cyclic nucleotide biosynthetic process, cyclic purine nucleotide metabolic process, regulation of cyclic nucleotide metabolic process, and positive regulation of cyclase activity.

For Bevacizumab, the output of 72 genes was generated that interacted with each other, which were involved majorly in leukocyte migration, regulation of positive chemotaxis, and Fc receptor signaling pathway, phosphatidylinositol-mediated signaling, inositol lipid-mediated signaling, positive regulation of MAPK cascade, and cell migration.

For Chloroquine, the output of 25 genes was generated that interacted with each other, which were involved majorly in the glutathione metabolic process, glutathione transferase activity, peptide metabolic process, and cellular amide metabolic process, cellular modified amino acid metabolic process, and glutathione derivative metabolic process.

For hydroxychloroquine, the output of 29 genes was generated that interacted with each other, that were involved majorly in the regulation of interleukin-8-production, interleukin-8 production, positive regulation of defense response, regulation of cytokine biosynthetic process, positive regulation of cytokine biosynthetic

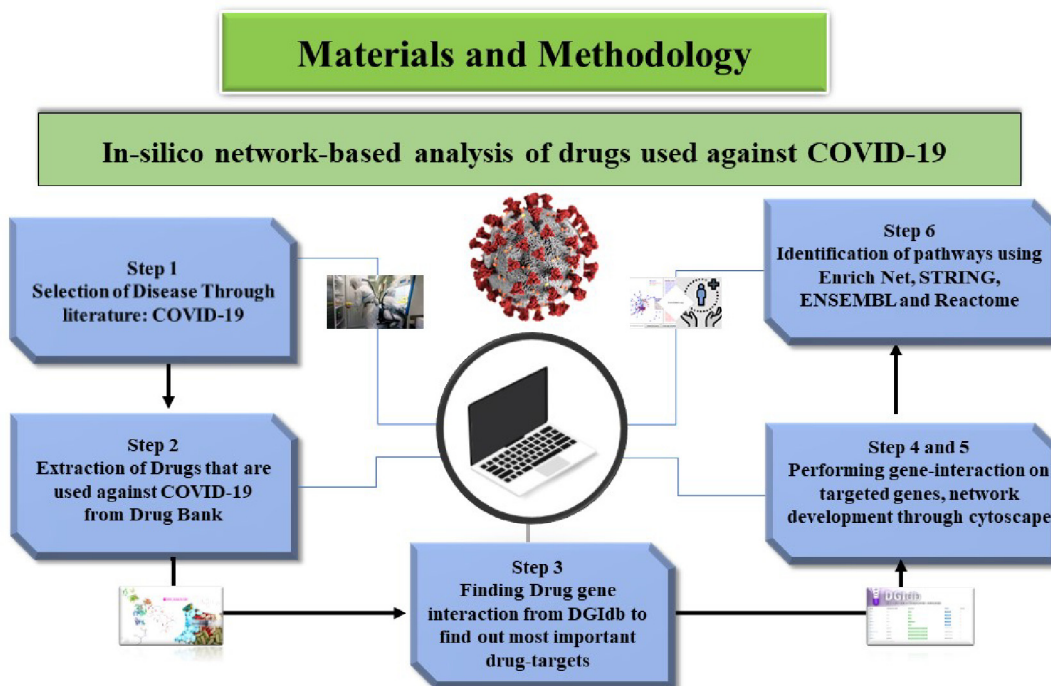


Fig. 1. The schematic diagram shows the overall methodology adopted for the work include drug extraction, drug-gene interaction, gene-gene interaction, and pathway analysis.

Table 1

The drugs that are used against COVID-19 are listed with type, group, weight, and chemical formulae.

No	Accession No	Drugs Name	Type	Group	Weight	Chemical formula
1.	DB00207	Azithromycin	Small Molecule	Approved	Average: 748.9845 Monoisotopic: 748.508525778	$C_{38}H_{72}N_2O_{12}$
2.	DB00112	Bevacizumab	Biotech	Approved, Investigational	149000.0 Da	$C_{6538}H_{10034}N_{1716}O_{2033}S_{44}$
3.	DB00608	Chloroquine	Small Molecule	Approved, Investigational, Vet approved	Average: 319.872 Monoisotopic: 319.181525554	$C_{18}H_{26}ClN_3$
4.	DB01611	Hydroxychloroquine	Small Molecule	Approved	Average: 335.872 Monoisotopic: 335.176440176	$C_{18}H_{26}ClN_3O$
5.	DB01601	Lopinavir	Small Molecule	Approved	Average: 335.872 Monoisotopic: 335.176440176	$C_{18}H_{26}ClN_3O$

process, cytokine biosynthetic process, and cytokine metabolic process.

For lopinavir, the output of 23 genes were generated that were interacted each other, which were involved mainly in the bile acid and bile salt transport, bile acid metabolic process, monocarboxylic acid transport, cell chemotaxis, organic anion transmembrane transporter activity, apical part of the cell and sodium-independent organic anion transport.

The set of genes obtained through GeneMANIA were cross-validated by using the EnrichNet tool to estimate the clear functional association between the genes. Enrichment analysis was applied over a set of genes of drug-gene and gene-gene interaction genes. For Azithromycin, 23 genes were uploaded, and seven pathways/processes were identified. For Bevacizumab, 58 genes were uploaded, and 17 pathways/processes were identified; for Chloroquine, 23 genes were uploaded, and six pathways/processes were identified; for hydroxychloroquine, 21 genes were uploaded, and 11 pathways/process were identified. For lopinavir, 16 genes were uploaded, and 13 pathways/processes were identified. Enrichment also generated network distance distribution (XD-score) and significance of overlap genes (Fisher-test, q-value). Gene identifier mapping was performed by enrichment analysis results presented in Table 3.

Table 3 shows the pathways and the processes in which the targeted genes were involved, and it was now clear that the genes that were targeted by the drug and the genes that were interacting with the drug-targeted-genes were involved in important functions of the body. The verification of the genes present in the network was also done and given in a supplementary file with gene identifier mapping. So, from the enrichment analysis results, to determine the pathways of the targeted and interacting genes of drugs for estimation of the functional association between them. The interaction of genes was the fact that genes work in coordination. Nevertheless, also enrichment provides scores to measure functional associations of the genes.

4. Discussion

In this research work, the network-based analysis was performed to check out the drugs' targeted pathways directly and indirectly. Azithromycin was extensively used (Gautret et al., 2020). However, sometimes side effects such as previous studies, diarrhea, gastrointestinal upset with abdominal pain, problems related to the peripheral nervous system, and nausea were documented by Hopkins (1991) and McMullan and Mostaghim (2015). For Azithromycin, we identified the most significant path-

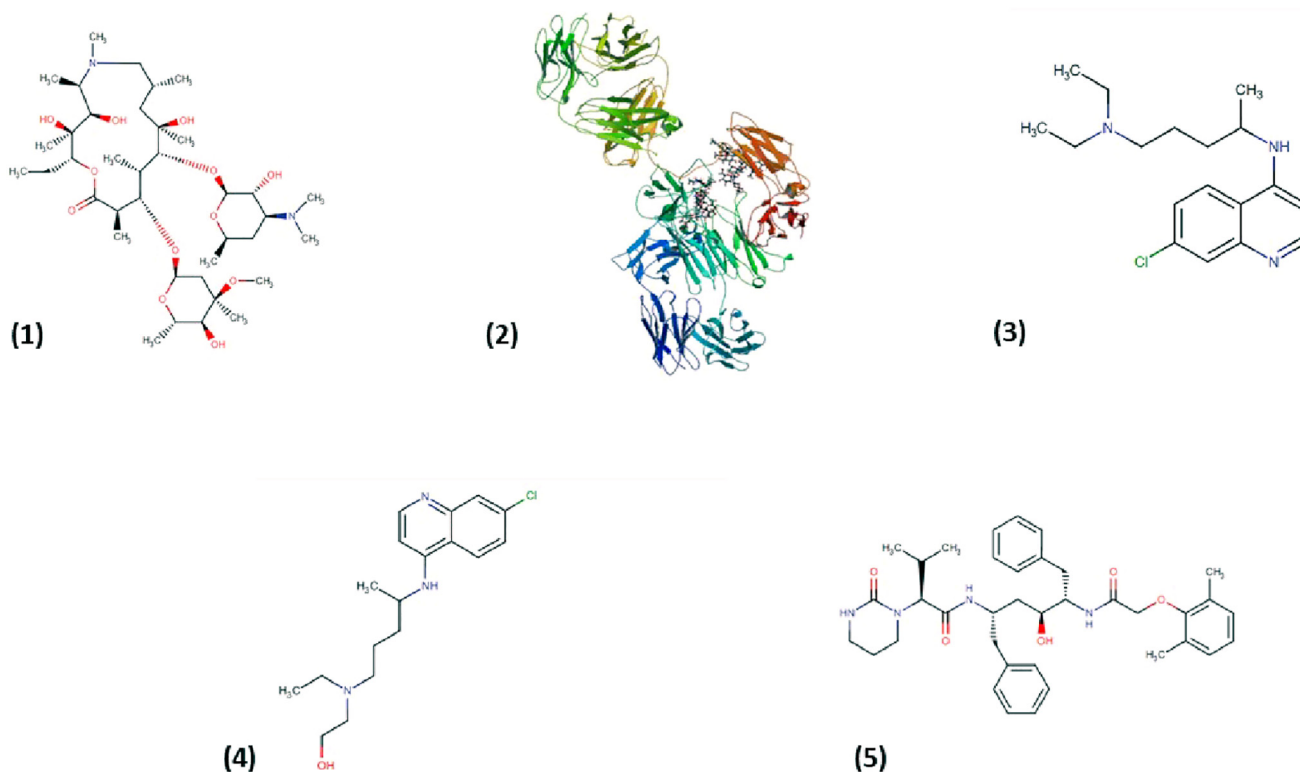


Fig. 2. Structures of the drugs retrieved from DrugBank. (1) Azithromycin (2) Bevacizumab a Protein-Based Therapy (3) Chloroquine (4) Hydroxychloroquine (5) Lopinavir for the treatment of COVID-19 caused by SARS-CoV-2.

Table 2
Drug gene interaction of selected drugs shows its interaction with targeted genes.

S. No	Drugs	Number of Targeted genes	Targeted genes list
1.	Azithromycin	9	MLNR, ADCYAP1R1, VIPR1, VIPR2, TFPI, NOS1, XDH, PADI4, ABCC1
2.	Bevacizumab	37	VEGFA, HTRA1, C1QB, TP53, THBS2, CXCR2, CTGF, VEGFB, ARMS2, HRAS, FCGR3A, ANXA11, VHL, F2R, PRL, COL18A1, ANGPT2, NF2, FCGR2B, MMP9, MYOD1, KRAS, FYN, EGFR, MTHFR, ERBB2, PIK3CA, C1QA, BRAF, NRG1, TP73, TERT, MMP2, PIK3CG, GGH, VEGFC, SHMT1, DPYD, FCGR2A, MET, TGM2, PTGES, FCGR1A, FCGR3B, CXCL8, KIT, NF1, NOS2, C1R, IDH1, C1QC, SLC19A1
3.	Chloroquine	5	MRGPRX1, TNF, GSTA2, G6PD, TLR9
4.	Hydroxychloroquine	9	F2R, TLR7, TLR9, PTGS2, IL1A, TNF, TLR3, APP, CYP2D6
5.	Lopinavir	3	CSAR1, SLCO1B1, ABCC2

ways to induce its effect by identifying twenty-nine genes representing 94.07% of shared protein domains and 5.03% of genetic interactions. Takahashi et al. (2020) reported that azithromycin effect on only one ABCB1 gene encoded for P-glycoprotein transporter could be found in the pathway identified in our study (Takahashi et al., 2020)

Amawi et al. (2020) and Garcia et al. (2020) reported that Bevacizumab could be used as COVID-19 therapeutics. Bevacizumab has some potentially serious side effects like hypertension, thromboembolism, proteinuria (Amawi et al., 2020; Garcia et al., 2020).

Lu et al. (2020) also reported some other side effects like a rise in cardiovascular impediment, bleeding, delayed wound healing, and gastrointestinal events (Lu et al., 2020). Yang et al. (2008) mentioned that Bevacizumab shows its relatedness with only Vascular Endothelial Growth Factor Receptors VEGFRs. However, seventeen pathways identified in our study with seventy-two genes that represent 61.00% of co-expression, 16.37% physical interaction, 10.78% of the pathway, 8.87% of prediction, 6.09% genetic interactions, 3.07% co-localization, and 3.88% of shared protein domains will help the researchers and pharmaceuticals to overcome the side effects (Yang et al., 2008).

Presently, a minimum of eighty trials of Chloroquine, hydroxychloroquine singly, or in combination with other drugs have been conducted globally (Ferner and Aronson, 2020; Khan et al., 2020). However, many complications have been reported, including ocular complications, majorly corneal deposits by Jorge et al. (2018), cardiovascular side effects, skin complications, neurological side effects, liver side effects, gastric or peptic ulcer complications by Ponticelli and Moroni (2017). A study on these drugs shows its impact on CYP2C8, SLC01B1, CYP2D6, and SLC01A2, and likewise, we identified six pathways for Chloroquine with twenty-five genes so that the effects of the drug can be induced. The identified pathways represent 13.50% of co-expression, 67.64% physical interaction, 4.35% of the pathway, 6.35% of prediction, 1.40% genetic interactions, 6.17% co-localization, and 0.59% of shared protein domains. Eight pathways and twenty-nine genes identified for hydroxychloroquine represent the 35.13% of co-expression, 1.54% physical interaction, 19.92% of the pathway, and 8.29% of prediction, 1.40% genetic interactions, 1.87% co-localization, and 35.25% of shared protein domains.

For lopinavir in the medical care of COVID-19, no benefits were observed, but it did show some secondary points of benefits (Cao et al., 2020; Stower, 2020). Several complications have been

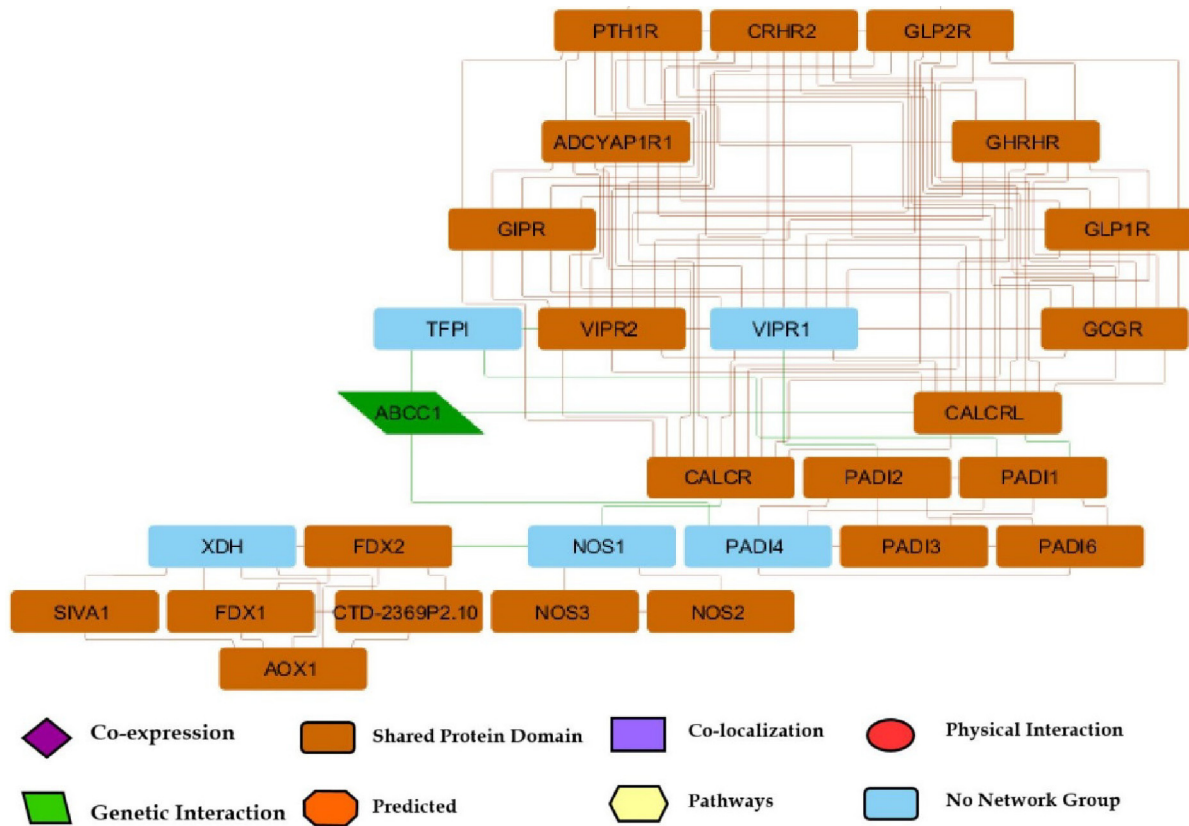


Fig. 3. Represents the 94.07% of shared protein domains and 5.03% genetic interactions shown by colored lines for Azithromycin.

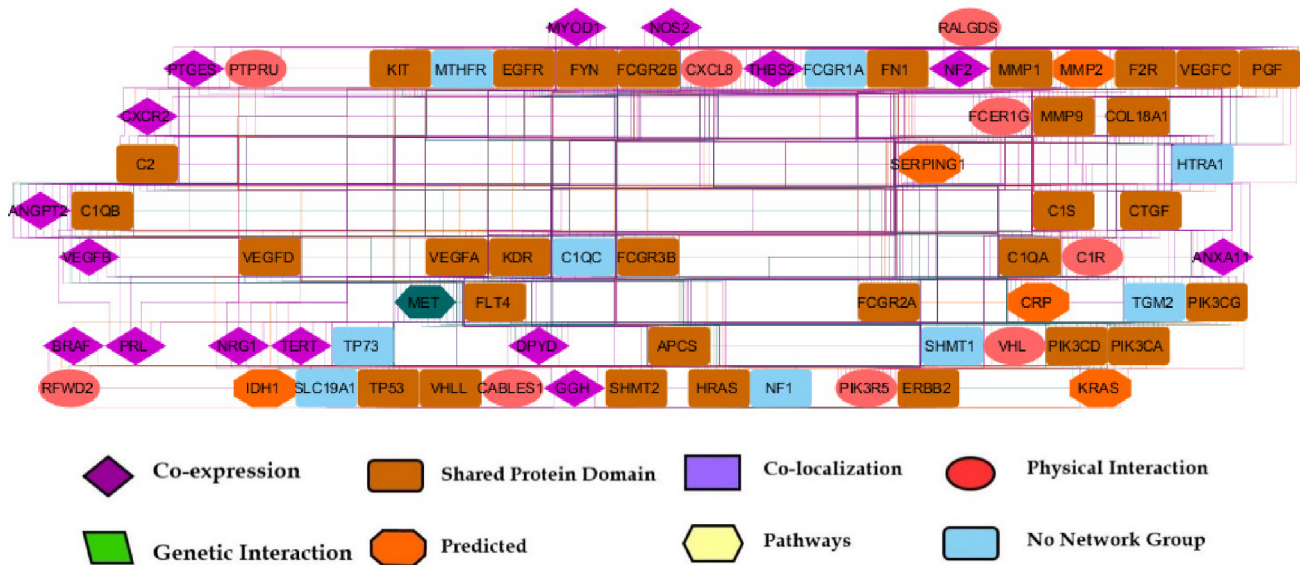


Fig. 4. Represents the 61.00% of co-expression, 16.37% physical interaction, 10.78% of the pathway, 8.87% of prediction, 6.09% genetic interactions, 3.07% co-localization, and 3.88% of shared protein domains shown by colored lines for Bevacizumab.

reported with lopinavir by [Arabi et al. \(2018\)](#) like gastrointestinal adverse events, including anorexia, nausea, abdominal discomfort, or diarrhea, as well as two serious adverse events, both severe gastritis and the ability to interact with multiple drugs due to the prohibition of CYP3A were well documented ([Arabi et al., 2018](#); [Cao](#)

[et al., 2020](#)). Here we identified thirteen pathways for lopinavir, with 23 drug targeted genes representing the 13.50% of co-expression, 67.64% physical interaction, 4.35% of the pathway, and 6.35% of prediction, 1.40% genetic interactions, 6.17% co-localization, and 0.59% of shared protein domains.

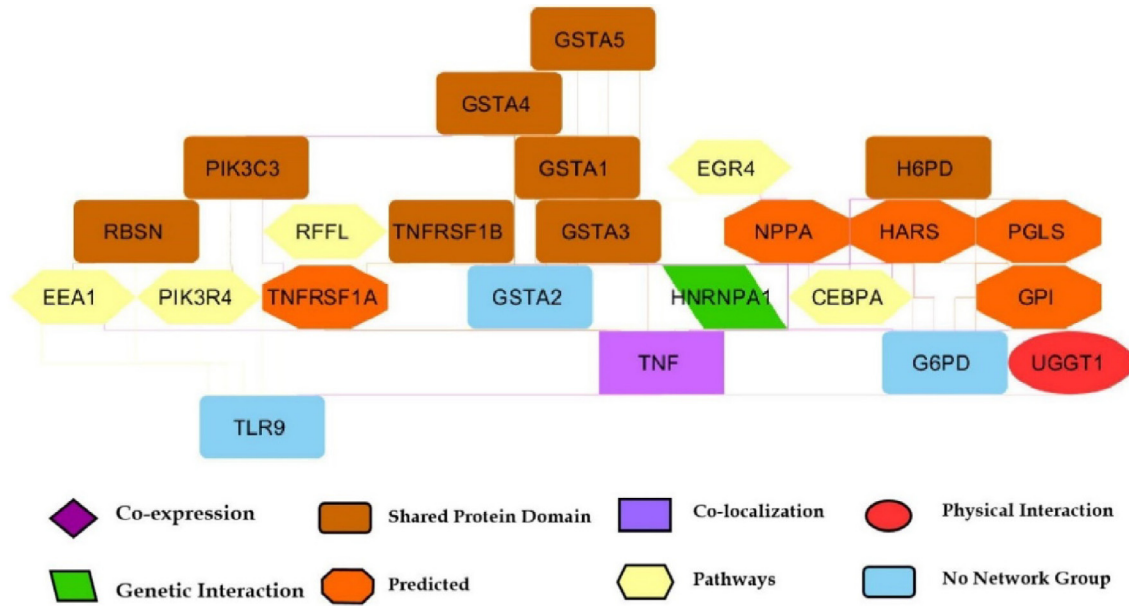


Fig. 5. Represents the 13.50% of co-expression, 67.64% physical interaction, 4.35% of the pathway, 6.35% of prediction, 1.40% genetic interactions, 6.17% co-localization, and 0.59% of shared protein domains shown by colored lines for Chloroquine.

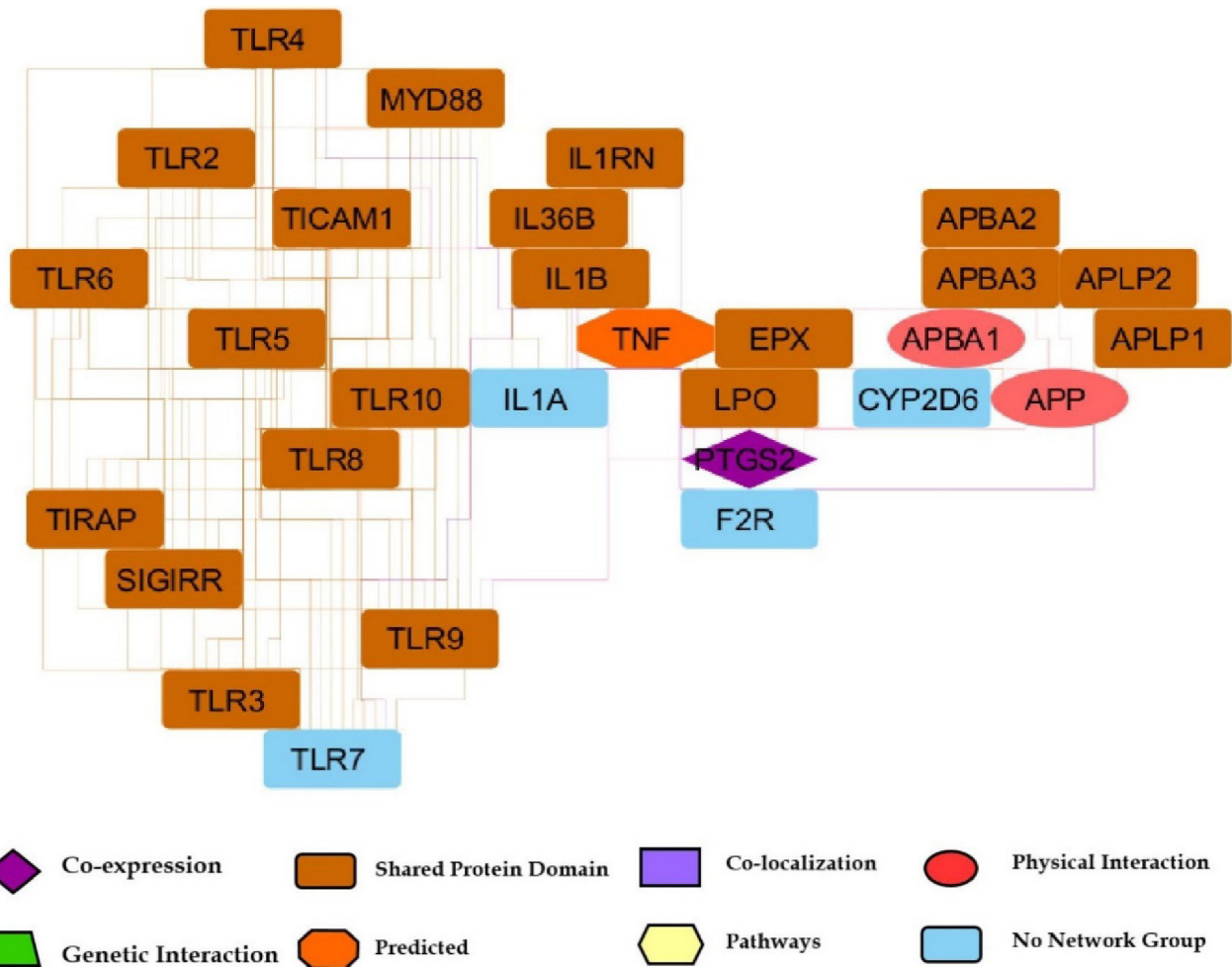


Fig. 6. Represents the 35.13% of co-expression, 1.54% physical interaction, 19.92% of the pathway, 8.29% of prediction, 1.40% genetic interactions, 1.87% co-localization, and 35.25% of shared protein domains shown by colored lines for hydroxychloroquine.

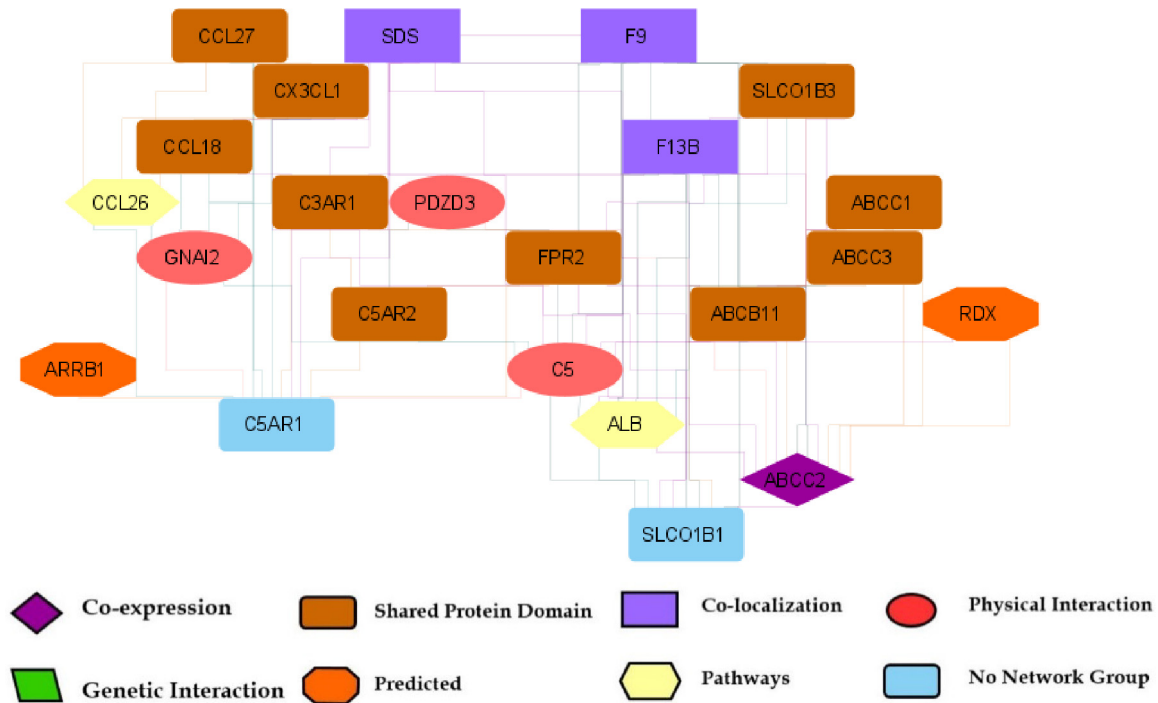


Fig. 7. Represents the 13.50% of co-expression, 67.64% physical interaction, 4.35% of the pathway, 6.35% of prediction, 1.40% genetic interactions, 6.17% co-localization, and 0.59% of shared protein domains shown by colored lines for lopinavir.

Table 3

For Azithromycin, Bevacizumab, Chloroquine, hydroxychloroquine and lopinavir set of genes were uploaded, and pathways/process are identified that shows different XD-Score, Fisher-test values, q-values, data sizes and overlapped genes with symbols.

No.	Annotation (pathway/process)	Significance of network distance distribution (XD-Score)	Significance of overlap (Fisher-test, q-value)	Dataset size (pathway gene set)	Dataset size (overlap genes)
Azithromycin					
1	GLUCAGON TYPE LIGAND RECEPTORS Dataset size (overlap genes)	2.1497 ADCYAP1R1, GCGR, GLP1R, GLP2R, GIPR, GHRHR, VIPR2, VIPR1	1.6e-11 23	33	8 genes
2	CLASS B2 SECRETIN FAMILY RECEPTORS Dataset size (overlap genes)	1.1326 ADCYAP1R1, GCGR, CRHR2, GLP1R, GLP2R, PTH1R, GIPR, CALCR, GHRHR, VIPR2, VIPR1	3.9e-13 23	85	11 genes
3	CALCITONIN LIKE LIGAND RECEPTORS Dataset size (overlap genes)	0.8679 CALCR	1.0e+00 23	10	1 gene
4	METABOLISM OF NITRIC OXIDE Dataset size (overlap genes)	0.7861 NOS3	1.0e+00 23	11	1 gene
5	PROSTANOID HORMONES Dataset size (overlap genes)	0.7861 ABCC1	1.0e+00 23	11	1 gene
6	G ALPHA S SIGNALLING EVENTS Dataset size (overlap genes)	0.7728 GCGR, CRHR2, GLP1R, GLP2R, PTH1R, CALCR, VIPR2, VIPR1, ADCYAP1R1, GIPR, GHRHR	1.3e-11 23	123	11 genes
7	GS ALPHA MEDIATED EVENTS IN GLUCAGON SIGNALLING Dataset size (overlap genes)	0.3012 GCGR	1.0e+00 23	27	1 gene
Bevacizumab					
1	INITIAL TRIGGERING OF COMPLEMENT Dataset size (overlap genes)	4.0527 C2, C1S, C1QB, C1QA, C1R, C1QC	3.00E-07	13	6 genes
2	SIGNALING BY VEGF Dataset size (overlap genes)	3.9898 VEGFA, VEGFC, KDR, FLT4, PGF	3.40E-06	11	5 genes
3	COMPLEMENT CASCADE Dataset size (overlap genes)	2.5989 C2, C1S, C1QB, C1QA, C1R, C1QC	3.20E-06	20	6 genes
4	GRB2 EVENTS IN EGFR SIGNALING Dataset size (overlap genes)	1.9758 HRAS, EGFR, KRAS	6.60E-03	13	3 genes
5	P38MAPK EVENTS Dataset size (overlap genes)	1.9758 HRAS, KRAS, RALGDS	6.60E-03	13	3 genes
6	TIE2 SIGNALING Dataset size (overlap genes)	1.8989 HRAS, KRAS, ANGPT2, PIK3CA	8.50E-04	18	4 genes
7	SIGNALING TO P38 VIA RIT AND RIN Dataset size (overlap genes)	1.8274 HRAS, BRAF, KRAS	7.20E-03	14	3 genes
8	COLLAGEN MEDIATED ACTIVATION CASCADE Dataset size (overlap genes)	1.6131 PIK3R5, PIK3CA, FCER1G, FYN	1.50E-03	21	4 gene
9	FRS2 MEDIATED ACTIVATION Dataset size (overlap genes)	1.5864 HRAS, BRAF, KRAS	9.60E-03	16	3 genes

Table 3 (continued)

No.	Annotation (pathway/process)	Significance of network distance distribution (XD-Score)	Significance of overlap (Fisher-test, q-value)	Dataset size (pathway gene set)	Dataset size (overlap genes)
10	GAB1 SIGNALOSOME Dataset size (overlap genes)	1.5352 PIK3CA, EGFR	7.80E–02	11	2 genes
11	SHC MEDIATED SIGNALLING Dataset size (overlap genes)	1.3989 HRAS, KRAS	8.90E–02	12	2 genes
12	PLATELET ADHESION TO EXPOSED COLLAGEN Dataset size (overlap genes)	1.2835 FCER1G, FYN	9.40E–02	13	2 genes
13	SHC RELATED EVENTS Dataset size (overlap genes)	1.2835 HRAS, KRAS	9.40E–02	13	2 genes
14	SOS MEDIATED SIGNALLING Dataset size (overlap genes)	1.2835 HRAS, KRAS	9.40E–02	13	2 genes
15	SIGNALLING TO ERKS Dataset size (overlap genes)	0.9577 HRAS, KRAS, BRAF, RALGDS	7.20E–03	34	4 genes
16	SIGNALLING TO RAS Dataset size (overlap genes)	0.9373 HRAS, KRAS, RALGDS	3.60E–02	26	3 genes
17	CD28 DEPENDENT PI3K AKT SIGNALING Dataset size (overlap genes)	0.8462 PIK3CA, FYN	1.90E–01	19	2 genes
Chloroquine					
1	GLUTATHIONE CONJUGATION Dataset size (overlap genes)	2.618 GSTA1, GSTA2, GSTA5, GSTA3, GSTA4	1.40E–06	17	5 genes
2	TOLL LIKE RECEPTOR 9 CASCADE Dataset size (overlap genes)	1.537 PIK3R4, TLR9, PIK3C3, EEA1	3.20E–04	23	4 genes
3	DEATH RECEPTOR SIGNALLING Dataset size (overlap genes)	1.356 TNF, TNFRSF1A	5.50E–02	13	2 genes
4	PHASE II CONJUGATION Dataset size (overlap genes)	0.734 GSTA5, GSTA3, GSTA4, GSTA1, GSTA2	3.40E–04	59	5 genes
5	PI3K CASCADE Dataset size (overlap genes)	0.721 TLR9, PIK3C3, PIK3R4	2.50E–02	36	3 genes
6	DOWNSTREAM SIGNALING OF ACTIVATED FGFR Dataset size (overlap genes)	0.63 TLR9, PIK3C3, PIK3R4	3.20E–02	41	3 genes
Hydroxychloroquine					
1	MYD88 CASCADE Dataset size (overlap genes)	4.2152 TLR6, TLR10, TLR5, TIRAP, SIGIRR, TLR9, TLR4, TLR2, TLR8	9.8e–17 21	19	9 genes
2	ACTIVATED TLR4 SIGNALLING Dataset size (overlap genes)	3.8651 TLR6, TLR10, TLR5, TIRAP, TICAM1, SIGIRR, TLR9, TLR4, TLR2, TLR8	5.5e–18 21	23	10 genes
3	TOLL LIKE RECEPTOR 9 CASCADE Dataset size (overlap genes)	3.4738 TLR6, TLR10, TLR5, TIRAP, SIGIRR, TLR9, TLR4, TLR2, TLR8	6.50E–16	23	9 genes
4	TOLL LIKE RECEPTOR 4 CASCADE Dataset size (overlap genes)	3.2854 TLR10, TLR5, TIRAP, TICAM1, SIGIRR, TLR9, TLR6, TLR4, TLR2, TLR8	2.00E–17	27	10 genes
5	VIRAL DSRNA TLR3 TRIF COMPLEX ACTIVATES RIP1 Dataset size (overlap genes)	1.4521 TICAM1, TLR3	4.10E–02	12	2 genes
6	JNK PHOSPHORYLATION AND ACTIVATION MEDIATED BY ACTIVATED HUMAN TAK1 Dataset size (overlap genes)	1.4521 TICAM1, TLR3	4.1e–02	12	2 genes
7	ACTIVATED TAK1 MEDIATES P38 MAPK ACTIVATION Dataset size (overlap genes)	1.3367 TICAM1, TLR3	4.3e–02	13	2 genes
8	HUMAN TAK1 ACTIVATES NFKB BY PHOSPHORYLATION AND ACTIVATION OF IKKS COMPLEX Dataset size (overlap genes)	1.1521 TICAM1, TLR3	5.30E–02	15	2 genes
9	TOLL RECEPTOR CASCADES Dataset size (overlap genes)	1.1168 TICAM1, SIGIRR, TLR9, TLR6, TLR5, TLR10, TIRAP, TLR3, TLR4, TLR2, TLR8	2.5e–14	85	11 genes
10	INNATE IMMUNITY SIGNALING Dataset size (overlap genes)	0.8949 TICAM1, SIGIRR, TLR9, TLR6, TLR5, TLR10, TIRAP, TLR3, TLR4, TLR2, TLR8	2.40E–13	105	11 genes
11	PROSTANOID HORMONES Dataset size (overlap genes)	0.7702 PTGS2	1.00E+00	11	1 gene
12	DEATH RECEPTOR SIGNALLING Dataset size (overlap genes)	0.6444 TNF	1.0e+00 21	13	1 gene
Lopinavir					
1	RECYCLING OF BILE ACIDS AND SALTS Dataset size (overlap genes)	1.6047 ABCB11, ABCC3	0.0491	11	2 genes
2	GAMMA CARBOXYLATION TRANSPORT AND AMINO TERMINAL CLEAVAGE OF PROTEINS Dataset size (overlap genes)	0.8683 F9	1.0000	10	1 gene
3	PROSTANOID HORMONES Dataset size (overlap genes)	0.7865 ABCC1	1.0000	11	1 gene
4	METABOLISM OF BILE ACIDS AND BILE SALTS Dataset size (overlap genes)	0.635 ABCB11, ABCC3	0.1433	27	2 genes
5	G ALPHA Z SIGNALLING EVENTS Dataset size (overlap genes)	0.6112 GNAI2	1.0000	14	1 gene
6	SYNTHESIS OF BILE ACIDS AND BILE SALTS VIA 7ALPHA HYDROXYCHOLESTEROL Dataset size (overlap genes)	0.5683 ABCB11	1.0000	15	1 gene

(continued on next page)

Table 3 (continued)

No.	Annotation (pathway/process)	Significance of network distance distribution (XD-Score)	Significance of overlap (Fisher-test, q-value)	Dataset size (pathway gene set)	Dataset size (overlap genes)
7	FORMATION OF FIBRIN CLOT CLOTTING CASCADE Dataset size (overlap genes)	0.5308 F9, F13B	0.1758	32	2 genes
8	INTRINSIC PATHWAY Dataset size (overlap genes)	0.4977 F9	1.0000	17	1 gene
9	SYNTHESIS OF BILE ACIDS AND BILE SALTS Dataset size (overlap genes)	0.4420 ABCB11	1.0000	19	1 gene
10	REGULATION OF INSULIN SECRETION BY FREE FATTY ACIDS Dataset size (overlap genes)	0.4420 GNAI2	1.0000	19	1 gene
11	COMPLEMENT CASCADE Dataset size (overlap genes)	0.4183 C5	1.0000	20	1 gene
12	REGULATION OF INSULIN SECRETION BY ACETYLCHOLINE Dataset size (overlap genes)	0.3969 GNAI2	1.0000	21	1 gene
13	ADP SIGNALLING THROUGH P2Y PURINOCEPTOR 12 Dataset size (overlap genes)	0.3969 GNAI2	1.0000	21	1 gene

This study demonstrates that each drug's pathways in which targeted genes and drugs play a significant role. It will help experts to overcome and deal with the side effects caused by these drugs.

5. Conclusion

From the aforementioned discussion and results, it was concluded that the genes targeted by a particular drug and the other genes that were interacting with the drug-targeted-genes were combined and perform some functions mentioned in the pathway/processes. After taking the specific medicine, if any side effects or complications are related to the function/pathway listed in the table for each drug then *in-silico* prediction is that the drug is the cause of these side effects.

Our study will help *in-vitro* experts overcome the side effects caused by Azithromycin, Bevacizumab, Chloroquine, Hydroxychloroquine, and lopinavir; this study explored the *in-silico* gene analysis for the COVID-19 drugs. Also mentioned are the possible drug targets that are genes and other genes that interact with them and show pathway/action performed by those genes in the human body.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sjbs.2021.01.006>.

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