

Retraction

Retracted: Computer-Aided Prediction and Identification of Phytochemicals as Potential Drug Candidates against MERS-CoV

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

- (1) Discrepancies in scope
- (2) Discrepancies in the description of the research reported
- (3) Discrepancies between the availability of data and the research described
- (4) Inappropriate citations
- (5) Incoherent, meaningless and/or irrelevant content included in the article
- (6) Manipulated or compromised peer review

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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- [1] H. S. Mahrosh, M. Tanveer, R. Arif, and G. Mustafa, "Computer-Aided Prediction and Identification of Phytochemicals as Potential Drug Candidates against MERS-CoV," *BioMed Research International*, vol. 2021, Article ID 5578689, 7 pages, 2021.

Research Article

Computer-Aided Prediction and Identification of Phytochemicals as Potential Drug Candidates against MERS-CoV

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The Middle East respiratory syndrome coronavirus (MERS-CoV) is the major leading cause of respiratory infections listed as blueprint of diseases by the World Health Organization. It needs immediate research in the developing countries including Saudi Arabia, South Korea, and China. Still no vaccine has been developed against MERS-CoV; therefore, an effective strategy is required to overcome the devastating outcomes of MERS. Computer-aided drug design is the effective method to find out potency of natural phytochemicals as inhibitors of MERS-CoV. In the current study, the molecular docking approach was employed to target receptor binding of CoV. A total of 150 phytochemicals were docked as ligands in this study and found that some of the phytochemicals successfully inhibited the catalytic triad of MERS-CoV. The docking results brought novel scaffolds which showed strong ligand interactions with Arg178, Arg339, His311, His230, Lys146, and Arg139 residues of the viral domains. From the top ten ligands found in this study (i.e., rosavin, betaxanthin, quercetin, citromitin, pluviatilol, digitogenin, ichangin, methyl deacetylnomilate, kobusinol A, and cyclocalamin) based on best *S*-score values, two phytochemicals (i.e., pluviatilol and kobusinol A) exhibited all drug-likeness properties following the pharmacokinetic parameters which are important for bioavailability of drug-like compounds, and hence, they can serve as potential drug candidates to stop the viral load. The study revealed that these phytochemicals would serve as strong potential inhibitors and a starting point for the development of vaccines and proteases against MERS-CoV. Further, *in vivo* studies are needed to confirm the efficacy of these potential drug candidates.

1. Introduction

Middle East respiratory syndrome (MERS) is a lethal respiratory syndrome caused by MERS coronavirus (MERS-CoV). In 2012, a 60-year-old man with lung failure in Jeddah, Saudi Arabia, was diagnosed with this syndrome. First time, in 2012, MERS-CoV was isolated from a 60-year-old Saudi male who died from severe respiratory failure [1]. MERS epidemic affected many countries with more severity (affected 1083 individuals in 23 countries) [2]. Viruses from the coronavirus family cause major respiratory and intestinal infections in animals and have been considered pathogenic to humans after the outbreak of SARS epidemic in 2002 and 2003 in China and MERS in 2012 in Saudi Arabia. SARS virus uses

an ACE2 enzyme as the receptor and affects the ciliated bronchial epithelial cells [3]. MERS-CoV targets dipeptidyl peptidase 4 (DPP4) and affects the unciliated bronchial epithelial cells [2].

MERS-CoV uses the machinery of the host cell and creates the copies of its genome in the cytoplasm of the host cell using its replication machinery. CoV completes its life cycle in four steps as S protein mediated cellular fusion and interaction with DPP4, expression of replicase for the replication, and transcription and release of virions [4]. DPP4 is directly linked with the human immune system, expressed on the cell surface and involved in various processes such as signal transduction, apoptosis, regulators for T-cell activation, regulation and cleavage of peptidase hormones, and

neuropeptides [5]. DPP4 is expressed on the epithelial and endothelial cell surface of human organs [6]. In addition to bat, recently, camel has also been found as an intermediate host of the MERS-CoV, and this discovery has attracted the attentions of scientists as the gene fragments and neutralizing antibodies have been reported from the camels in May 2015 [7]. From the recent studies, it has been found that the MERS-CoV receptor-binding domains interact easily with the DPP4 of the bat with no hindrance and restriction at the cellular level [8].

MERS-CoV virus affects the host cells by binding to the cellular receptor DPP4 via the S1 subunit and secondly by the formation of the fusion core by the S2 subunit [9]. The main mechanism of MERS-CoV is its binding to DPP4 on the cell surface that causes the mutations in human membranous glycoproteins and in mammals (i.e., camels). Human MERS-CoV virus differs from the camel MERS-CoV on the basis of their nucleotide sequences. MERS-CoV has some strategies to escape from antiviral responses as the virus contains many structural and nonstructural proteins that modulate the host immune and antiviral defence proteins. Combination therapy with ribavirin and beta-interferon has been used for early-stage patients, but in the future, it might be possible that the use of antiviral and combination therapy would be proven fruitful against MERS-CoV [10]. Recently, the implication of computational biology has opened a new door in the vicinity of drug designing. Molecular docking is a key technique to foresee the binding capacity and interactions of ligands to design drugs. The current study was therefore planned to target nonstructural protein (nsp13) of MERS-CoV and docked with plant phytochemicals to explore potential drug candidates against the virus.

2. Materials and Methods

A ready-to-dock library of 140 phytochemicals was prepared and docked against MERS-CoV nsp13 via the Molecular Operating Environment (MOE) software. MOE is a comprehensive suite specifically designed for protein/DNA modelling, protein structure analysis, drug designing, peptide modelling, molecular docking, and stimulations.

2.1. Ligand Database Preparation. An extensive literature study was performed to hunt for antiviral compounds from different medicinal plants with potential activity against different viral diseases. The chemical structures of all the phytochemicals were downloaded from the PubChem database (<http://www.ncbi.nlm.nih.gov/pccompound>) and saved in the MOE database after energy minimization.

2.2. Refinement of Receptor Protein. The three-dimensional (3D) structure of the MERS-CoV nsp13 was retrieved from the Protein Data Bank (PDB) using PDB ID 5WWP (<http://www.rcsb.org/pdb>) and optimized by removal of water molecules, addition of hydrogens, 3D protonation, and energy minimization using MOE.

2.3. Molecular Docking. The docking algorithm of MOE was used to dock a prepared ligand database with an active site of the MERS-CoV nsp13 receptor protein. A siteFINDER tool

was used to find the binding residues with default parameters such as rescoring 1: London dG, retain: 10, refinement: force field, rescoring 1: London dG, and retain: 10 to predict the interactions of ligands with active residues of the MERS-CoV nsp13. After docking, the S-score was the criteria to select the appropriate confirmations between ligands and receptor protein.

2.4. Drug Scan. A drug scan of selected phytochemicals was executed following the “Lipinski rule of five” (<http://www.scbio-iitd.res.in/software/drugdesign/lipinski.jsp>) in order to assure the appropriate molecular properties of the ligands as potential drug candidates. These rules predict the druggability of selected candidates on the bases of molecular mass (≤ 500 Dalton), hydrogen bond donors (< 5), hydrogen bond acceptors (< 10), molar refractive index (40-130), and $\log P$ (≤ 5) [11]. Evaluation of ADMET-based properties (i.e., absorption, distribution, metabolism, excretion, and toxicity) classifies the likeness and substructure recognition of lead compounds. Therefore, to further validate the potential and bioavailability of selected hits, all the compounds were subjected to the admetSAR server [12]. The admetSAR facilitates researchers to freely predict the ADMET properties of drug molecules from the perspective of medical chemistry.

3. Results

3.1. Molecular Docking. The library of 140 compounds was docked against nsp13 of MERS-CoV using MOE. Out of 140 docked ligands, only top 10 ligands with the best S-scores and binding patterns with interactive amino acid residues of the hotspot conserved regions of the binding pocket were selected for further analysis. MOE provides multiple conformations of each phytochemical, and on the basis of the minimum S-score, top 10 selected phytochemicals were rosavin, betaxanthin, quercetin, citromitin, pluviatilol, digitogenin, ichangin, methyl deacetylnomilinate, kobusinol A, and cyclocalamin. Details of each ligand including their S-scores, RMSD values, and interacting residues are shown in Table 1.

3.2. Interaction Analysis. Among the top 10 selected ligands, rosavin with the minimum S-score of -15.40 showed potential hydrophobic interactions with binding residues (i.e., Arg339, Asn361, Lys146, and Cys309) of the active site of the receptor protein. In this study, Arg339 was reported as the main interactive amino acid residue in all the interactions except for pluviatilol, ichangin, and cyclocalamin. Interactions between the ligands and the binding residues of the receptor protein are given in Table 1.

Rosavin showed interactions with four amino acid residues (i.e., Arg339, Asn361, Lys146, and Cys309) of the receptor protein (Figure S1). Rosavin is an O-acyl carbohydrate extracted from the plant *Rhodiola rosea* used as dietary herb for stress relief, CNS stimulation, and mental disorders. Betaxanthin has shown interactions with Arg339, His311, and Lys146 of the MERS-CoV nsp13 protein (Figure S2). Betalains are Tyr-derived plant pigments which provide red-violet (betacyanins) and yellow (betaxanthins) colours to

TABLE 1: Interaction of top ten phytochemicals with MERS-CoV nps13.

Sr. no.	PubChem ID	Compound name	S-score	RMSD value	Residues
1	9823887	Rosavin	-15.40	1.64	Arg339, Asn361, Lys146, Cys309
2	135926572	Betaxanthin	-14.64	2.45	Arg339, His311, Lys146
3	5280343	Quercetin	-14.24	1.13	Arg339, Arg139, Arg390, His230
4	12303287	Citromitin	-13.73	1.33	Arg339, Arg139, Thr382
5	70695727	Pluviatilol	-13.01	1.14	Arg560, Val533, His554, Pro514, Asn516
6	441886	Digitogenin	-13.15	0.83	Arg339, Arg139, Glu143, Lys146, Asn361
7	441801	Ichangin	-12.99	2.52	Arg202, Tyr205, Thr532, Asn177
8	272822441	Methyl deacetylnomilate	-12.45	2.17	Arg339, Arg139
9	274366689	Kobusinol A	-12.25	1.30	Arg339, Arg139, Asn361, His311
10	13857944	Cyclocalamin	-12.34	1.04	Arg139, Asn179, Lys146

TABLE 2: Pharmacokinetic parameters important for bioavailability of compounds' drug-likeness properties of selected phytochemicals.

Sr. no.	Ligand	Mass (<500 D)	HBD (≤ 5)	HBA (≤ 10)	Log P (<5)	Molar refractivity (40-130)	Violations
1	Rosavin	428	6	10	2.75	101.31	1
2	Betaxanthin	358	2	6	1.71	84.39	0
3	Quercetin	302	5	7	0.52	64.36	0
4	Citromitin	404	0	8	3.56	99.23	0
5	Pluviatilol	356	1	6	3.10	90.31	0
6	Ichangin	488	1	9	4.54	125.39	0
7	Digitogenin	448	3	5	6.06	140.22	2
8	Methyl deacetylnomilate	504	2	9	4.81	128.66	1
9	Kobusinol A	374	2	6	3.07	97.76	0
10	Cyclocalamin	502	1	9	4.90	130.08	1

HBD: hydrogen bond donors; HBA: hydrogen bond acceptors; log P : the logarithm of octanol/water partition coefficient.

fruits and vegetables. Betacyanins are heterocyclic plant pigments reported with antioxidant activity.

Quercetin is a polyphenolic flavonoid. It is a potential chemopreventive and anti-inflammatory agent and has been reported from various plants including *Allium cepa*, *Ginkgo biloba*, *Malus domestica*, and Buckwheat tea. Quercetin showed interactions with Arg339, Arg139, Arg390, and His230 residues of the viral protein (Figure S3). Similarly, citromitin interacted with Arg339, Arg139, and Thr382 residues of the receptor protein (Figure S4). Citromitin belongs to the family of organic compounds known as 8-o-methylated flavonoids. Citromitin is a hexamethoxyflavanone and has been reported as the major chemical constituent of *Citrus*.

Ichangin belongs to the sesquiterpenoid class of terpenes. It showed interactions with Arg202, Tyr205, Thr532, and Asn177 (Figure S5). Digitogenin is a steroidal saponin and also called as 2- α -hydroxy steroid, 3- β -hydroxy, or 15- β -hydroxy steroids. Digitogenin has been extracted from the plant *Digitalis purpurea* and reported with potential membrane-related applications such as antihyperlipidemia. Digitogenin exhibited interactions with Arg339, Arg139, Glu143, Lys146, and Asn361 residues of the viral protein (Figure S6). Methyl deacetylnomilate showed interactions with Arg339 and Arg139 of the receptor protein (Figure S7). Methyl deacetylnomilate belongs to the class of citrus limonoids present in lime, citrus, and grapefruit and has

been reported as an anti-inflammatory and anticancer agent. Cyclocalamin belongs to the class of organic compound known as steroid lactone. Cyclocalamin has been extracted from citrus and mandarin orange (tangerine). Cyclocalamin showed binding interactions with Arg139, Asn79, and Lys 146 of the receptor protein (Figure S8).

In the light of the current results, it is assumed that these natural phytochemicals would be proven as good antagonists against MERS-CoV (nsp13) protein to stop its proliferation in the future. Results also demonstrated the potency of these selected ligands as they can block the target site of the viral replicative nonstructural protein. The results from the interactions of ligands and target protein elucidate that these phytochemicals would be strong drug candidates against the MERS-CoV nsp13.

3.3. Drug Scan. The Lipinski rule of five (Ro5) illustrates the durability of potential drug candidates. According to this rule, the molecular mass of the molecule should be ≤ 500 Dalton, high lipophilicity should be expressed as $\log P < 5$, hydrogen bond donors should be ≤ 5 , hydrogen bond acceptors should be ≤ 10 , molar refractivity should be between 40 and 130. Only those that accomplished all five parameters could be proven as potential drug candidates. Among the top 10 ligands selected in this study, all ligands except methyl deacetylnomilate and cyclocalamin followed the Ro5. The

TABLE 3: ADMET profiling of the best selected phytochemicals.

	Rosavin	Betaxanthin	Quercetin	Citromitin	Pluviatilol	Ichangin	Digitogenin	MD	Kobusinol A	Cyclocalamin
Absorption										
BBB	-	+	-	-	+	+	+	+	+	+
HIA	-	+	+	+	+	+	+	+	+	+
Caco-2 permeability	-	-	-	+	+	-	-	-	+	+
PGS	NS	Substrate	NS	NS	NS	Substrate	NS	Substrate	NS	Substrate
PGI	NI	NI	NI	Inhibitor	Inhibitor	NI	NI	Inhibitor	Inhibitor	Inhibitor
ROCT	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Metabolism										
CYP3A4 substrate	Substrate	Substrate	Substrate	Substrate	NS	Substrate	Substrate	Substrate	Substrate	Substrate
CYP2C9 substrate	Substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS
CYP2D6 substrate	NS	NS	NS	Substrate	Substrate	NS	NS	NS	Substrate	NS
CYP3A4 inhibition	NI	NI	Inhibitor	Inhibitor	Inhibitor	Inhibitor	NI	Inhibitor	NI	Inhibitor
CYP2C9 inhibition	NI	NI	NI	NI	Inhibitor	NI	NI	NI	Inhibitor	NI
CYP2C19 inhibition	NI	NI	NI	Inhibitor	Inhibitor	NI	NI	NI	Inhibitor	NI
CYP2D6 inhibition	NI	NI	NI	NI	Inhibitor	NI	NI	NI	NI	NI
CYP1A2 inhibition	NI	NI	Inhibitor	Inhibitor	Inhibitor	NI	NI	NI	Inhibitor	NI
Toxicity										
AMES toxicity	NAT	NAT	NAT	NAT	NAT	NAT	NAT	NAT	NAT	NAT
Carcinogens	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC

MD: methyl deacetylnomilinate; BBB: blood-brain barrier; HIA: human intestinal absorption; PGS: P-glycoprotein substrate; PGI: P-glycoprotein inhibitor; ROCT: renal organic cation transporter; NS: nonsubstrate; NI: noninhibitor; NAT: non-Ames toxic; NC: noncarcinogenic.

drug assessment test also revealed fewer adverse effects of the selected ligands. Rosavin, methyl deacetylnomilinate, and cyclocalamin violated only one rule, so on the basis of overall drug profiling, these ligands could also be accepted as good drug candidates (Table 2).

ADMET properties of drug molecules were checked after the durability. All the selected top ten ligands accomplished the criteria of being good drug candidates as they are nontoxic and noncarcinogenic. Rosavin, betaxanthin, and citromitin showed a little variation, but the overall results could be accepted as they are nontoxic (Table 3).

The interactions and binding patterns of the best phytochemicals (i.e., pluviatilol and kobusinol A) with nsp13 of MERS-CoV are shown in Figures 1 and 2, respectively.

The fifth ligand pluviatilol is a principal lignan precursor from the class of polyphenol isolated from *Lindera obtusiloba*. Pluviatilol has been reported with antiallergic and anti-inflammatory activities. The binding patterns of pluviatilol showed interactions with Arg560, Val533, His554, Pro514, and Asn516 residues of the receptor protein.

4. Discussion

Middle East respiratory syndrome coronavirus (MERS-CoV) is a lethal zoonotic pathogen that causes severe respiratory illness which leads to respiratory and kidney failure. MERS-CoV was firstly reported in Saudi Arabia as a causative agent for respiratory and renal disease with approx. fatality rate of ~35%. In 2019, about 203 new cases of MERS were reported because there was no typical targeted vaccine for the MERS-CoV [13]. Most of the cases were associated with travellers, and predominately human-to-human associations and transmission were more common. Phylogenetic and epidemiological studies revealed bats as initial and camels as intermediate reservoirs for MER-CoV prevalence [14].

The phylogenetic study revealed a close relationship of MERS-CoV with the *Tylosycteris* bat coronavirus HKU4 and *Pipistrellus* bat coronavirus HKU5. This close genomic relationship suggests the zoonotic origin of MERS-CoV (from bat coronaviruses) [15]. Beta-coronavirus (β -CoV) are positive-strand RNA viruses that belong to the family of Coronaviridae and order Nidovirales. The genome of a

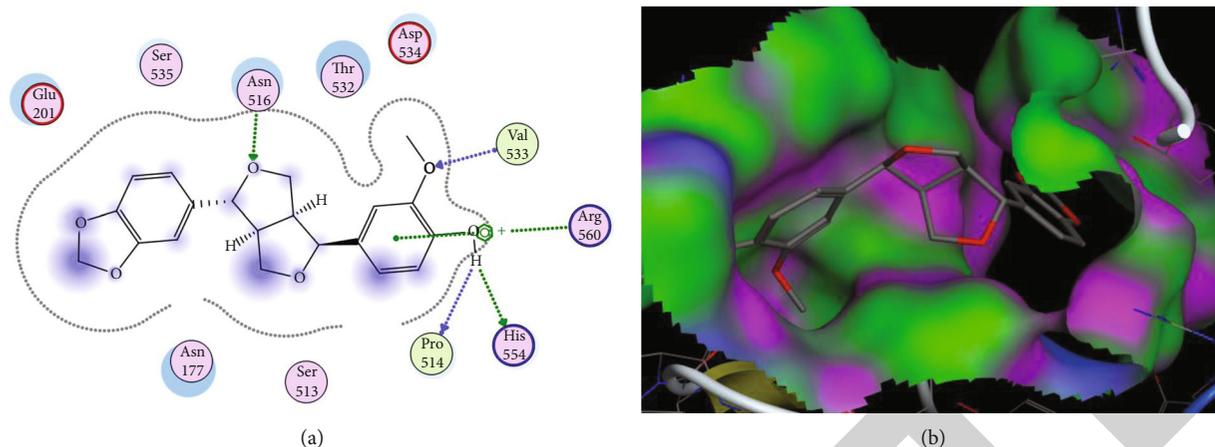


FIGURE 1: Interactions (a) and binding patterns (b) of pluviatilol with MERS-CoV nps13.

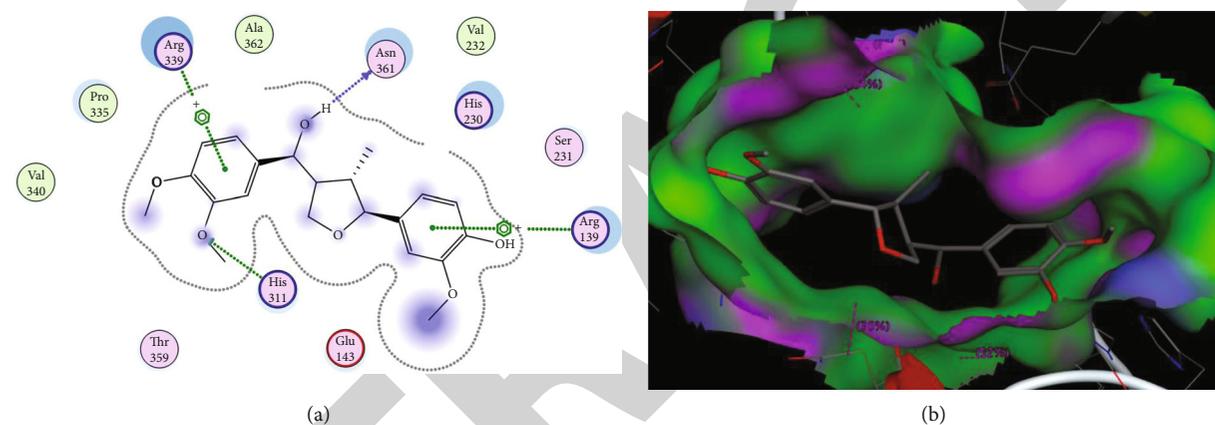


FIGURE 2: Interactions (a) and binding patterns (b) of kobusinol A with MERS-CoV nps13. Kobusinol A was the ninth ligand, and it showed interactions with Arg339, Arg139, Asn361, and His311 residues of the viral protein. Kobusinol A is a lignin and has been extracted from leaves of different plants, and it plays an important role as an antimicrobial agent against a variety of microbial diseases.

MERS-CoV encodes major structural and nonstructural proteins that mediate in viral replication and progression of the infection. The nsp13 used in this was also a nonstructural helicase of the MERS-CoV genome involved in multiple functioning. Spike glycoprotein displays a multidomain architecture and organized homodimer units that mediate the entry of the virus inside the host cell. The variety in sequence and structure of spike glycoprotein mediates virus to alter the mechanism of its fusion and attachment to the host receptors which leads towards the difficulty in targeting a specific site of the viral protein [14].

The domains in the spike protein are comprised of N-terminal and C-terminal. N-terminal subunits are comprised of folded domains that mediate viral attachment to DPP4 receptors in the host cell while C-terminal fuses the membranes of the virus with the host cell to provide spot for initiation of infection. Upon interaction with DPP4 on the epithelial cells, the virus infects the lungs of the host [16]. In the MERS-CoV genome, the 3-terminal genes encode proteins with structural and functional variability to make a complex which provides targets for antiviral agents. On the

other hand, the 5-terminal of the MERS-CoV genome is comprised of large open reading frames (i.e., ORF1a and ORF1b) which encode different nonstructural and structural proteins including spike, membrane, envelope, and nucleocapsid structural proteins [17].

Computational biology skills help scientists to evaluate the possibilities of binding patterns of different ligands before the experimental work in the laboratory [18]. Molecular docking is an elaborative method to discover the binding features of different small molecules as drugs against the target proteins [19–21]. The natural flora plays a vital role in drug screening and development [22–24]. The crude extracts of different medicinal plants have been reported with biologically active compounds with multiple clinical activities against many diseases [25, 26]. Biomedical or herbal decoction of many medicinal plants has been in practice since prehistoric times for management of multiple disorders [27]. For the past few years, medical plants have played an important role in the pharmaceuticals to treat many uncured diseases. Plants are good sources of phytochemicals that play role as inhibitors to the binding sites of the target moiety [28].

The purpose of this study includes the discovery of novel compounds as an antagonist of MERS-CoV nsp13. The MERS-CoV nsp13 is a nonstructural helicase that predominantly forms the core of membrane-bound replication-transcription complexes [29]. Extensive studies have been made to develop the vaccine against MERS-CoV, but the efforts have yet not proven successful. So, there is dire need to design new drugs against the virus.

The current study was based on the docking of different phytochemicals from different medicinal plants against the MERS-CoV nps13. The 3D structure of the target protein of Middle East respiratory CoV (human beta corona virus) was downloaded from PDB and saved in the MOE software after following the docking protocols. After docking, top 10 molecules were shortlisted on the bases of the best S-scores and interactions with amino acids at the active site of the viral protein using MOE software. Moreover, a detailed study for ADMET scanning of lead compounds was also carried out. All the selected compounds in this study showed no diverse effects in absorption in the human body. Distribution of a drug through the blood brain barrier is a key factor in the drug discovery as most of the drugs cannot cross the BBB due to the tight junctions around the brain [30]. Other types of models such as HIA (human intestine absorption), renal organic cation transporter, and P-glycoprotein substrate also help to evaluate the compounds as good drug candidates. Another model is comprised of the clusters of the isoenzyme cytochrome P50 involved in the metabolism of the drug, and 75% association of drug metabolism is linked with these enzyme clusters. From the results of the admetSAR screening, all the selected phytochemicals were found as nontoxic and noncarcinogenic.

From the results of interacting amino acid residues, Arg178, Arg339, His311, His230, Lys146, and Arg139 have been found as more common interacting residues in this study. In the chemical interactions, Arg339 and Arg139 as basic and directly interacting residues shared the common side chain position. Results demonstrated the potential of these ligands to bind and block the target site of the viral protein. It can be concluded that these 10 molecules can be used as drugs in the future with no severe side effects.

5. Conclusion

Beta coronavirus is the main causative agent of the Middle East respiratory syndrome, and instead of many contributions by scientists, no accurate drug against MERS-CoV has been discovered since its emergence. Through molecular docking, scientists find the potency of many natural compounds to act as drugs against disease causative agents. The present study discovered 10 strongly interacting phytochemicals (i.e., rosavin, betaxanthin, quercetin, citromitin, pluviatilol, digitogenin, ichangin, methyl deacetylnomilate, kobusinol A, and cyclocalamin) from different medicinal plants against MERS-CoV, and out of these two phytochemicals (i.e., pluviatilol and kobusinol A), all Ro5 and pharmacokinetic parameters were followed. On the bases of chemical interactions and drug scanning of these molecules, it was revealed that they would inhibit MERS-CoV replica-

tion. The aim of this study was to figure out the novel bioactive compounds from medicinal plants with the maximum potential to inhibit the target viral protein which could be used as efficient drug candidates against the MERS-CoV nps13.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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Supplementary Materials

The supplementary file contains the interactions and binding patterns of rosavin, betaxanthin, quercetin, citromitin, ichangin, digitogenin, methyl deacetylnomilate, and cyclocalamin with nps13 of MERS-CoV (Figures S1–S8, respectively). (*Supplementary Materials*)

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